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Saving mothers and babies for the new world

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Saving mothers and babies for the new world

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Editorial: Saving mothers and babies for the new world

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perinatal care, obstetrics, neonatology, fetal, perinatal mortality

Editorial on the Research Topic
Saving mothers and babies for the new world

Introduction

First, where or what is the *New World*? Historically, this refers to the region of the Americas. In this context, the *New World* is the future of humankind, an ambiguous borderless phenomenon that is informed and built upon from lessons of its past and from stories of triumph and regrets; of innovations, experiences of the pandemic, economic successes, and failures; of those unwanted wars; and of great science. The *New World* we envision emphasizes the quintessential of actions to ensure human survivability, by prioritizing equitable care to mothers and babies regardless of their region. Positive outcomes for mothers and babies can only be achieved by ensuring that healthcare professionals are knowledgeable, holistic, ethical, and safe and that effective execution of ethically robust healthcare policies and guidelines for equitable perinatal healthcare is adequately supported. These aims need to be at the forefront of policies of governments across all countries in the *New World* despite all setbacks. With this in mind, the research topic *Saving Mothers and Babies for the New World* accepted 16 diverse full-length articles and collected abstracts presented at the 21st Federation of Asia Oceania Perinatal Societies (FAOPS) Congress that provided a wealth of information and science that can help carve future research and inform policies.

The crystal ball: accurate data can help predict adverse perinatal outcomes

The rich diversity found in large databases from developing countries can help predict various pregnancy-related problems. Hypertension is a leading medical problem encountered during pregnancy with profound effects to both the mother and her baby. Zhang et al. appraised the accuracy of the LASSO regression dynamic prediction model in

predicting the four subtypes of hypertensive disorder in pregnancy (HDP). The predictive capability was above 85%, with the highest being close to 92%, accurately predicting the risk of these four subtypes. In the review of 13 studies by Sukor et al. they concluded that endothelial function was impaired in the offspring of women with *de novo* HDP. The need to study and monitor the cardiovascular health of these affected infants, whether they are predisposed to hypertension or ischemic heart disease in later life, brings to attention of neonatologists. Some complexities in monitoring the fetus during antenatal care (ANC) was shared by Saw et al. who discovered that using the Hadlock and INTERGROWTH-21 chart in the Malaysian population may result in misdiagnoses of fetuses that are small for gestational age (SGA). Moreover, a differential accuracy in predicting preterm SGA according to trimester, with poorer accuracy in the second trimester, is found. Qiu et al. demonstrated that microtia is the subject to scrutiny. It is often accompanied by congenital defects of other organs and structures, especially the heart and face. Hence, prenatal diagnosis of microtia and associated anomalies by ultrasound is of important clinical significance.

Teamwork and safety: collaborative management and safe perinatal interventions

Two case reports in this collection further highlight the importance of concerted perinatal efforts to achieve better outcomes. Sun et al. described an interesting case management of parturients with acute myocardial infarction resulting in positive successful outcomes for both the mother and the fetus through multidisciplinary team management, consisting of obstetricians, cardiologists, anesthetists, and pediatricians. Yantao et al. narrated a pregnancy complication called Meckel's diverticulum, which is a condition that is not easily diagnosed. Once it is highly suspected, especially with peritonitis, surgical emergency helps save the life of the mother and the baby. In this special issue, reports on techniques that improve perioperative care and therapeutic advances in reproductive care include a randomized comparative trial conducted by Pang et al. This group reported that epidural dexmedetomidine was a better alternative to standard-dose epidural fentanyl in reducing the mean hourly amount of ropivacaine administered and minimizing opioid-related side effects in women who needed labor analgesia. Regarding postpartum care, Lizheng Zhao and Hong Wei recommended to strengthen the Enhanced Recovery After Surgery (ERAS) guideline and cooperation among researchers in order to generate a broader consensus and results and ultimately provide help for cesarean section recovery. An interesting observation by **Huang et al.** concentrated on the relationship between cervical length (CL) and massive intraoperative bleeding in patients with placenta accreta spectrum (PAS). They found that when the CL was greater than 33 mm, the risk of bleeding decreased by 44%. Therefore, CL is capable of functioning as a standalone parameter to identify the risk of massive intraoperative bleeding during cesarean section in patients with suspected PAS. Within the community in the Tibetan Plateau region, Long et al. found that vaginal delivery for term breech in the lithotomy position was less safe than cephalic presentation. Timely recognition of problems and availability of cesarean section greatly improved the safety.

Back to basics, be kind: good perinatal care and zero abuse required

Proper and effective perinatal care, from fertility preservation to conception and careful ANC, is crucial in ensuring a healthy pregnancy outcome. **Han et al.** questioned whether the function of reproductive organs of a woman with adenomyosis can be preserved and looked into the treatment of adenomyosis in relation to infertility. The authors advised that an individualized strategy based on the grading and needs of the patient is required to achieve pregnancy. **Chilot et al.** lamented on the relatively low frequency of optimal ANC utilization in countries with high maternal mortality. It was found that both individual-level factors and community-level factors were significantly associated with ANC utilization. This provided appropriate guidance and basis for targeted prevention of adverse outcomes with improved care. The emphasis on not only physical health of the woman but also protection of their mental health, as well as individualizing treatment, is certainly timely, in order to achieve a satisfactory reproductive outcome. In this context, Gebeyehu et al. found a high prevalence of disrespect and abuse of women during childbirth in East Africa. Predictors of maternal disrespect and abuse include instrumental delivery, childbirth complications, receiving care at government hospitals and a poor wealth index.

Strategize: preventing preterm births and neonatal deaths

The rate of preterm births has not improved in the past decade, and prematurity remains as one of the leading causes of perinatal and neonatal deaths. According to the World Health Organization (WHO), this is translated to an estimated 13.4 million babies born preterm in 2020 with nearly 1 million dying from complications related to prematurity. This is an area to focus on if we are to achieve the sustainable development goal (SDG) target 3.2 that aims to prevent deaths of newborns and children under 5 years of age by 2030. Sub-Saharan Africa is one of the regions with the highest number of preterm births. A retrospective follow-up study of Girma et al. in Ethiopia reported that nearly one in three preterm neonates (32.1%) will die with a mean survival time of 18.7 days. The two major predictors of death are respiratory distress syndrome and perinatal asphyxia. On a positive note, preterm infants who received kangaroo mother care (KMC) are much less likely to die. In mitigating the high mortality rates of preterm infants in low- and middle-income countries (LMIC),

KMC or skin-to-skin contact nursing may be a solution. Previously, KMC has been targeted to caring of the stable-growing preterm infant. However, the WHO has recently launched new guidelines (November 2022) for immediate kangaroo mother care (iKMC) to improve survival of infants born preterm and having low birth weight. Infection during pregnancy is a recognized cause of preterm birth. Bacterial vaginosis (BV) has been reported as a risk factor for preterm labor although not many extensive studies have been conducted especially from the LMIC and study methods were variable. Ng et al. used a rapid point-of-care test based on a chromogenic response to increased sialidase in vaginal swab samples and detected one in 10 pregnant women to have BV, with variable rates depending on the method of detection used and the presenting symptoms. On this note, the authors highlighted that BV could be much higher (one in four or five) among women with preterm labor as was the case in two other studies they cited. Preterm birth below 34 weeks was almost four times more likely to be associated with BV. Consequently, neonatal morbidity was greater with twice more likely admissions to the neonatal intensive care unit because of respiratory problem requiring support. All the BV-positive pregnancies were treated with vaginal pessaries containing dequalinium chloride, which has a broad antimicrobial spectrum. Although the intervention did not appear to prolong the gestational period of the pregnancy to term, future research for this condition may provide us insights of its role in reducing preterm births.

Keep it going: ensuring sustainability of good practices

Positive outcomes require sustainability of good practices. In this issue, **Xu et al.** shared their model of multi-disciplinary *in situ* simulation training (MIST) in Shenzhen, China. Collaboration between neonatal and obstetric healthcare providers to conduct a weekly simulation training exhibited a significant reduction in neonatal asphyxia. More than one-third of the sessions included resuscitation of preterm neonates. Implementing such regular on-site simulation training should be considered in countries that encounter high rates of mortality in asphyxiated preterm infants. It is imperative that neonatal resuscitation and stabilization competency through workshops or courses such as Helping Babies Breathe, Neonatal Resuscitation Program (NRP), and S.T.A.B.L.E. are intensified in a global sense with pooling of resources and funding for training of personnel and basic infrastructure. The sustainability of such programs and the integration of simulation healthcare are much needed to ensure that health staff remain competent in saving lives.

The new world

The *New World* is right at our doorstep. Reducing maternal deaths and ensuring survival of even the littlest infant demand collective effort, not only from the perinatal health fraternity but also from every individual within. To save mothers and babies, we need accurate data, perform safe collaborative teamwork, practice quality perinatal care, launch effective preventive strategies, and ensure that all these practices are sustained for the future and the *New World*.

> *As mankind weeps,*
>
> *Therein lies the embrace,*
>
> *Of the mother and her baby,*
>
> *Where saving is our duty,*
>
> *For the new world's gates.*

Author contributions

AK: Writing – original draft, Writing – review & editing. FC: Writing – original draft, Writing – review & editing. HI: Writing – review & editing. RP: Writing – review & editing. DE: Writing – review & editing. ZM: Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Comparison of epidural dexmedetomidine to fentanyl in reducing ropivacaine dose in Programmed Intermittent Epidural Bolus plus Patient Controlled Epidural Analgesia during labor: A randomized, double-blind, controlled study

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Background: Dexmedetomidine has been documented to reduce the dose of both intrathecal local anesthetic during cesarean delivery, and the concentration of ropivacaine needed for inducing analgesia during labor. However, few studies have compared adjuvant dexmedetomidine to fentanyl on how they impact the dose of ropivacaine required during labor. The aim of the current study was to evaluate the efficacy of epidural dexmedetomidine at doses of 0.3, 0.4, or 0.5 and 2 μg/ml of fentanyl (the traditional clinical concentration), when added to epidural 0.125% ropivacaine.

Methods: This was a randomized, double-blinded study that comprised one hundred eighty-eight patients, allocated into four groups receiving either epidural fentanyl at 2 μg/ml, or dexmedetomidine at 0.3, 0.4, or 0.5 μg/ml for labor analgesia. The primary outcome was the amount of ropivacaine necessary per hour. Secondary outcomes included visual analogue pain scale (VAS), motor block (Bromage Scale), side effects, patient satisfaction, and neonatal outcomes.

Results: At the completion of the study, data from 165 participants were analyzed. The mean hourly amount of epidural ropivacaine administered was 16.2 ± 3.3, 14.0 ± 3.1, 13.1 ± 3.7 and 12.1 ± 2.5 ml/h in the 2 μg/ml fentanyl group, and the 0.3, 0.4 and 0.5 μg/ml dexmedetomidine groups, respectively. There was a significant difference among groups in the mean hourly consumption of epidural ropivacaine ($P < 0.0001$ for 1 way ANOVA). The frequency of PCEA (patient-controlled epidural analgesia) was significantly higher in the fentanyl group than in the three dexmedetomidine groups

($P < 0.001$), and similar among the dexmedetomidine groups. The mean values of the VAS among all groups were similar over time, $P > 0.05$. The incidence of pruritus in the fentanyl group was 17.5%, whereas no patient experienced pruritus in any of the dexmedetomidine groups, $P < 0.0001$.

Conclusion: The study demonstrated that epidural dexmedetomidine (0.3 and 0.4 μg/ml) was superior to standard dose epidural fentanyl in reducing the mean hourly amount of ropivacaine administered, and minimizing opioid-related side effects. Further large and multicenter studies would be necessary to confirm the benefits of dexmedetomidine, and potentially serve as an alternative to opioids for routine use in labor analgesia.

Clinical trial registration: [http://www.chictr.org.cn/showproj.aspx?proj=62846], identifier [ChiCTR2000039067].

KEYWORDS

dexmedetomidine, fentanyl, labor analgesia, epidural, ropivacaine

Introduction

Opioids are usually used in epidural labor analgesia to reduce the dose requirements of epidural local anesthetic agents, specifically intended to minimize the side effect of an epidural blockade, including maternal motor block and hypotension. However, epidural opioids are also associated with side effects, such as pruritus and reduced fetal heart rate variability (1). Therefore, non-opioid local analgesic adjuvants have been studied as a mean to reduce the quantity of epidural local anesthetic agents. The α_2 receptor agonist, dexmedetomidine, has been shown to provide opioid-sparing analgesia when administered peripheral, epidural, or intrathecal as an adjuvant (2–8).

In a prior study, dexmedetomidine decreased the EC_{50} (median effective concentration) of ropivacaine for inducing epidural labor analgesia at an optimal dose of 0.4 μg/ml (6). Nevertheless, there have been few studies that have assessed the efficacy of epidural dexmedetomidine as a local anesthetic adjuvant for labor analgesia via the model of Programmed Intermittent Epidural Bolus (PIEB) plus Patient Controlled Epidural Analgesia (PCEA).

The primary aim of the current study was to evaluate the efficacy of epidural dexmedetomidine at three different doses: 0.3, 0.4, or 0.5 μg/ml, compared to fentanyl at the traditional clinical concentration of 2 μg/ml, as adjuvants to epidural 0.125% ropivacaine. The secondary aims were to define the dose-response of epidural dexmedetomidine at doses ranging from 0.3 to 0.5 μg/ml, and assess the visual analogue pain scale (VAS), motor blockade (Bromage Scale), medication side effects, patient satisfaction, and neonatal outcomes. We therefore hypothesized that dexmedetomidine used as an analgesia adjuvant could reduce the mean hourly dose requirement of ropivacaine for PIEB plus PCEA during labor when compared to the combination of ropivacaine with fentanyl.

Methods

Design

The study was registered in the Chinese Clinical Trial Registry on 1st February, 2021 (registry number ChiCTR2000039067) prior to enrollment of the first patient (February 3, 2021); Ethical approval for this study (Ethical Committee No. LLSC-KYKT-2022-0002-A) was provided by the Ethical Committee of Lin-ping District Women and Children Care Hospital, Hangzhou, China (Chairperson Prof. Shen Yuejian) on January 17, 2021. Written, signed informed consent was obtained from all study subjects. This was a randomized, double-blinded study to assess the mean hourly requirement of ropivacaine administered, comparing the use of adjuvant fentanyl in standard doses to adjuvant dexmedetomidine in three different concentrations.

Subjects and setting

Recruited for this study were nulliparous parturients with healthy singleton pregnancies, gestational age ≥ 37 weeks, American Society of Anesthesiologists Physical Status II spontaneous onset of labor, latent phase of labor with cervical dilation of 2–5 cm, and painful contractions requiring labor epidural analgesia. Patients with preeclampsia or hypertension, preexisting or gestational diabetes, BMI > 35 kg/m^2, contraindications to local anesthetics, dexmedetomidine,

and fentanyl were excluded from this study. We enrolled 240 patients for initial eligibility assessment with a goal of 33 patients for each group for final analysis.

Study protocol

Patients were randomized into four groups to receive four adjuvant medications: 2 μg/ml fentanyl, or 0.3, 0.4, or 0.5 μg/ml dexmedetomidine (Dexmedetomidine Hydrochloride Injection, 2 ml: 200 μg, Yangtze River Pharmaceutical Group Co., Ltd., Jiangsu, China; preservative-free and contains no additives or chemical stabilizers), with the randomization scheme generated by FX. He was not involved in any clinical patient management, but did collect the study data, using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). The randomization scheme was kept in sequentially numbered opaque envelopes and opened after the first patient was enrolled. The study drugs were prepared in sterile conditions by an anesthesia assistant who had no involvement in clinical patient management. All study participants were blinded to their group assignment and the study drug administered.

Following parturient arrival in the labor room, a peripheral venous catheter was inserted and routine monitoring initiated (blood pressure cuff, pulse oximeter, electrocardiography leads, respiratory rate monitor, and fetal heart rate monitor). When the patient required labor analgesia, an epidural catheter (two holes, 19G; Shanghai SA Medical Technology Co., Ltd., Shanghai, China) was placed at the L3-4 interspace inserting 3–4 cm into the epidural space by 1 of 3 attending anesthesiologists (R-YP, Y-HS, and X-QJ). As a test dose, a combination of 45 mg lidocaine and 15 μg epinephrine, was injected through the catheter.

After a satisfactory test dose, the patient received 10–13 ml of study solution as an epidural bolus to relieve the labor pain. If the patient reported a visual analogue pain scale (9) (VAS) value > 3 on a 0–10 scale (0, no pain; 10, worst imaginable pain) 20 min following the epidural bolus, the patient was excluded from this study because the epidural catheter was regarded as an "unreliable" catheter (subsequently to be replaced or managed by the anesthesiologist).

Forty-five minutes following injection of the initial epidural study bolus, a PIEB plus PCEA infusion protocol was initiated using an Apon infusion pump (Jiangsu Apon Medical Technology Co., Ltd., Jiangsu, China) according to the following parameters: PIEB analgesia was initiated with an 8 ml bolus and maintained using a programmed bolus of 8 ml at 40 min intervals; additionally, 8 ml PCEA boluses were available for supplementation with a 15 min lockout interval, and maximum dose of 30 ml/h. Patients experiencing "breakthrough pain" were treated with a bolus of 10 ml of 0.25% ropivacaine plus 100 μg of fentanyl according to our institutional practice. If the patient still reported a VAS > 3 after a bolus or required yet an additional bolus in 1 h, she was excluded from the study.

The primary outcome of this study was the mean amount of ropivacaine administered per hour, which was defined as the total amount administered (consumption) of 0.125% ropivacaine volume divided by the infusion duration. Secondary outcomes were also studied as follows: the number of PCEA boluses the patient used; the values of VAS recorded at the following time-points: prior to epidural catheter placement, 20 min following the initial induction bolus, and subsequently at 2 h intervals until delivery; the motor block level as assessed according to the Bromage scale (10) (0–3, 0 = ability to move all joints in the leg, 1 = able to bend the knees and ankles, 2 = only able to move the ankle, and 3 = not able to move any leg joint) 20 min after the initial induction bolus and then at 2 h intervals until delivery; the incidence of side effects including hypotension (a decrement > 20% from baseline blood pressure, or an absolute value <90 mm Hg; if hypotension occurred, the patient's position was changed to left lateral and the blood pressure was checked again; if hypotension persisted, ephedrine 5 mg was given intravenously and repeated as required), bradycardia (heart rate < 50 bpm, rescued by atropine 0.5 mg), pruritus, maternal sedation (none [awake and alert], mild [awake but drowsy], moderate [asleep but arousable], and severe [not arousable]), respiratory depression (oxygen saturation < 90%), nausea and vomiting, and shivering. Newborn umbilical artery pH, Apgar score at 1 and 5 min, and delivery mode (vaginal vs. cesarean delivery) were also recorded and analyzed. Patient satisfaction was also assessed using a 1–5 verbal score (1 = not satisfied at all, 5 = extremely satisfied).

Sample size

According to PASS (version 11.0.7; NCSS, LLC, Kaysville, UT, USA) software and prior studies, to detect a clinically meaningful difference of 20% in hourly ropivacaine consumption among groups ($\alpha = 0.05$ and $1-\beta = 0.8$), thirty-five subjects would be needed for each group (11). In order to account for attrition, the Institutional Review Board (IRB) agreed to the recruitment of 60 patients for each group.

Statistical analysis

The distribution of univariate data was assessed via the Kolmogorov–Smirnov test. Normal distribution data such as the demographic data, the total hourly ropivacaine consumption, and pain scores were presented as Mean ± SD and analyzed via one-way analysis, and the Tukey's multiple comparisons test was used for pairwise comparison. Non-normal distribution data was presented as Median (range) and tested with the Kruskal–Wallis test, and the *post hoc* Dunn's test was applied to analyze the pairwise comparison. Categorical trend data such as incidence of side effects and Bromage score were analyzed

using the Cochran–Armitage chi-square test for trend, if an overall test of difference among groups was significant, chi-square tests were used for pairwise comparison. $P < 0.05$ was considered significant. Where Bonferroni corrections were applied, adjusted P values are presented. Analyses were performed using IBM SPSS Statistics for Windows version 22.0 (IBM Corp, Armonk, NY, USA) and GraphPad Prism version 5.0 (GraphPad Software Inc., San Diego, CA, USA).

Results

Of the initial 240 participants enrolled with written informed consent, data from 165 participants were involved in the final analysis (Figure 1). Patient demographic data are shown in Table 1 and there was no significant difference among groups. There were no significant differences among the groups in the progress of labor, neonatal outcomes. Totally, there were 11 patients who underwent cesarean delivery in the four groups. Two patients in 0.4 and 0.5 μg/ml dexmedetomidine groups because of fetal distress, and a patient in 0.4 μg/ml dexmedetomidine group underwent cesarean delivery because of fetal macrosomia. Eight patients in the four groups underwent cesarean delivery because of cephalopelvic disproportion. There was no significant difference in the cesarean delivery rate among groups.

The mean hourly consumption of epidural ropivacaine was 16.2 ± 3.3, 14.0 ± 3.1, 13.1 ± 3.7 and 12.1 ± 2.5 ml/h in the 2 μg/ml fentanyl group, and the 0.3, 0.4, and 0.5 μg/ml dexmedetomidine groups, respectively. There was a significant difference among groups in the mean hourly consumption of epidural ropivacaine ($P < 0.0001$ for 1 way ANOVA, Figure 2). Tukey's multiple comparisons test for mean hourly consumption of epidural ropivacaine showed there was a significant difference between the 2 μg/ml fentanyl group and the other three dexmedetomidine groups (adjusted $P = 0.0205$, 0.0002, and < 0.0001, respectively); no significant difference existed among dexmedetomidine groups. Totals of 82.5% (33/40), 44.6% (17/39), 44.4% (20/45) and 22.0% (9/41) of patients in 2 μg/ml fentanyl, 0.3, 0.4, and 0.5 μg/ml dexmedetomidine group required additional PCEA. The frequency of PCEA boluses were 3 (1, 3), 0 (0, 2), 0.5 (0, 2) and 0 (0, 1) for 2 μg/ml fentanyl, 0.3, 0.4, and 0.5 μg/ml dexmedetomidine group; and there was significantly higher in the 2 μg/ml fentanyl group than in the other three dexmedetomidine groups ($P < 0.001$) and similar in the dexmedetomidine groups (Table 2). Totals of 37.5% (15/40), 17.9% (7/39), 15.6% (7/45) and 12.2% (5/41) of patients in 2 μg/ml fentanyl, 0.3, 0.4, and 0.5 μg/ml dexmedetomidine group suffered "breakthrough pain"; the incidence of "breakthrough pain" was significant higher in group 2 μg/ml fentanyl than in other groups, all adjusted $P < 0.05$. The mean value of VAS scores among groups was similar over time ($P > 0.05$, Figure 3). Pain scores showed relief 20 min following epidural injection in all four groups. Although patient satisfaction of pain relief was significantly different among groups ($P = 0.002$), the overall mean satisfaction score was > 4.0 (1–5). Patients in the fentanyl group had a mean satisfaction value of 4.2, whereas patients in the 0.3, 0.4, and 0.5 μg/ml dexmedetomidine groups had mean values of 4.8, 4.7, and 4.8, respectively.

The incidence of pruritus in the fentanyl group was 17.5%; in contrast, no patient experienced pruritus in any of the dexmedetomidine groups, $P < 0.001$. There was a significant difference in Bromage score among groups, $P = 0.007$. Three patients had a Bromage score of 2 and six patients had

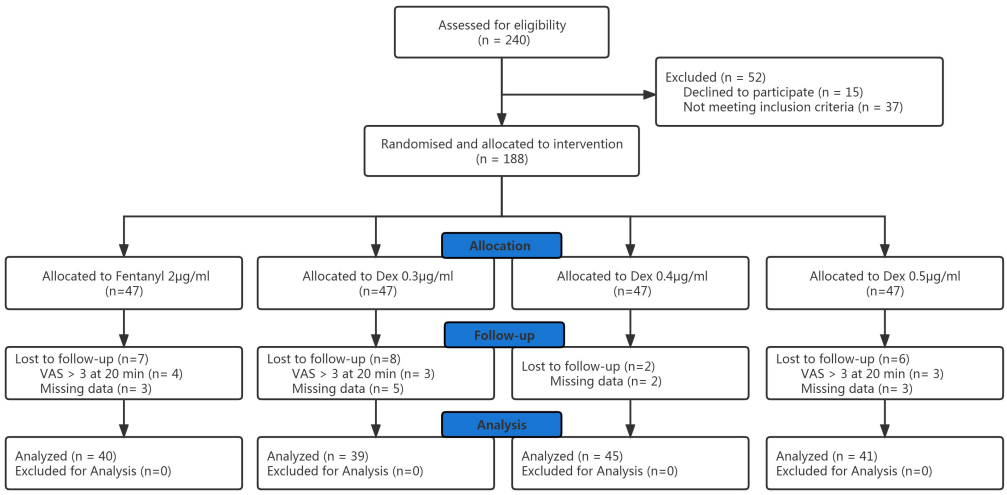

FIGURE 1
CONSORT diagram.

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TABLE 1 Demographics, labor characteristics, and neonatal outcomes of laboring patients.

	Fentanyl 2 μg/ml	Dexmedetomidine 0.3 μg/ml	Dexmedetomidine 0.4 μg/ml	Dexmedetomidine 0.5 μg/ml
Sample size, *n*	40	39	45	41
Age, years	27.6 ± 3.7	28.3 ± 3.7	27.4 ± 3.4	28.8 ± 3.5
BMI, kg/m^2	26.1 ± 3.0	27.5 ± 2.4	27.0 ± 3.2	27.2 ± 2.4
Gestational age, weeks	39.3 ± 1.1	39.3 ± 1.0	39.1 ± 1.0	39.5 ± 2.0
Cervical dilation at epidural placement, cm	2.1 ± 0.3	2.2 ± 0.4	2.2 ± 0.4	2.1 ± 0.4
Epidural analgesia to cervix complete, min	240 (160, 344)	195 (115, 316)	240 (156, 421)	220 (145, 300)
Epidural analgesia to delivery, min	293 (226, 401)	255 (176, 377)	307 (193, 502)	278 (188, 403)
Cesarean delivery, *n* (%)	2 (5.0)	2 (5.1)	4 (8.9)	5 (12.2)
Patient satisfaction score, 1–5	4.3 ± 0.8*	4.8 ± 0.4	4.7 ± 0.6	4.8 ± 0.5
Neonatal weight, g	3333 ± 373	3366 ± 425	3285 ± 433	3339 ± 408
1-min Apgar score	9.8 ± 0.5	9.7 ± 0.7	9.8 ± 0.5	9.7 ± 0.6
5-min Apgar score	9.9 ± 0.4	9.9 ± 0.2	10 ± 0.0	9.9 ± 0.4
Umbilical artery pH	7.29 ± 0.04	7.30 ± 0.03	7.30 ± 0.03	7.30 ± 0.04

Data was shown as Mean ± SD, median (interquartile range) and number (%) as appropriate. *Adjusted $P < 0.05$, compared with dexmedetomidine groups.

a Bromage score of 1 in the 0.5 μg/ml dexmedetomidine group; three patients had a Bromage score of 1 in the 0.4 μg/ml dexmedetomidine group; one patient in the 0.3 μg/ml dexmedetomidine group had a Bromage score of 1; 2 patients had a Bromage score of 1 in 2 μg/ml fentanyl group. There was no difference in the side effects of nausea and vomiting, shivering, severe sedation, and respiratory depression (Table 2).

Discussion

The results of the present study demonstrated that 0.3, 0.4 and 0.5 μg/ml of adjuvant dexmedetomidine reduced the mean hourly requirement of epidural ropivacaine in the standard PIEB plus PCEA infusion protocol for labor analgesia when compared to the use of the traditional epidural dose of 2 μg/ml of fentanyl; and with a lower frequency of pruritus. In the subgroup analysis, the mean hourly consumption of epidural ropivacaine was similar among the three different doses of dexmedetomidine. Although a dose-dependent reduction in local anesthetic consumption was not found, 0.5 μg/ml of dexmedetomidine combined with 0.125% ropivacaine was associated with a high degree of motor block in this study. Therefore, while our results confirmed that epidural adjuvant dexmedetomidine could reduce the dose requirement of epidural local anesthetic agent compared to fentanyl, we would advocate that the concentration of dexmedetomidine not be greater than 0.4 μg/ml when combined with 0.125% of ropivacaine for epidural labor analgesia.

From these data, it would seem appropriate to consider the use of adjuvant dexmedetomidine as an alternative to fentanyl to reduce the dose consumption of local anesthetic agents and further minimize the associated side effects. Recently, an opioid-free strategy for pain relief has been widely advocated by anesthesiologists with the purpose of decreasing opioid related side effects, potential for addiction, and to promote Enhanced Recovery after Surgery (12, 13). Although this study substantiated the superiority of dexmedetomidine to fentanyl in decreasing epidural ropivacaine and with less pruritus, larger studies would be appropriate to further compare the advantages and disadvantages of the two adjuvants before dexmedetomidine could be routinely preferred in clinical practice.

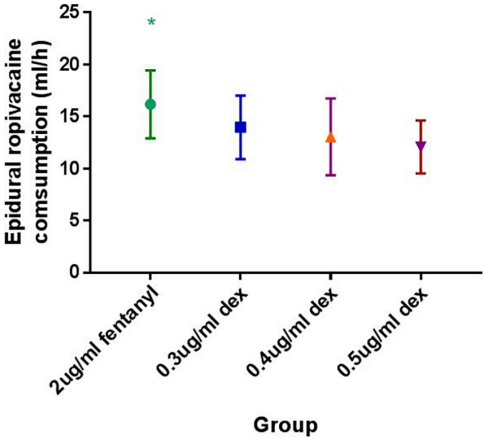

FIGURE 2
Mean hourly ropivacaine consumption between groups. *$P < 0.0001$ for one way ANOVA.

TABLE 2 Side effects and required patient-controlled epidural analgesia of epidural 2 μg/ml fentanyl verse three different concentrations of dexmedetomidine.

	Fentanyl 2 μg/ml	Dexmedetomidine 0.3 μg/ml	Dexmedetomidine 0.4 μg/ml	Dexmedetomidine 0.5 μg/ml	*P* value
Sample size	40	39	45	41	–
Pruritus	7 (17.5)*	0 (0.0)	0 (0.0)	0 (0.0)	<0.001
Bromage score > 1	2 (5.0)	1 (2.6)	3 (6.7)	9 (22.0)	0.007
Hypotension	5 (12.5)	3 (7.6)	5 (11.1)	7 (17.1)	0.635
Maternal Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Fetal bradycardia	2 (5.0)	5 (12.8)	3 (6.7)	2 (4.9)	0.483
Shivering	3 (7.5)	1 (2.6)	0 (0.0)	2 (4.9)	0.294
Severe Sedation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Nausea and vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Patient required PCEA	33 (82.5)*	17 (44.6)	20 (44.4)	9 (22.0)	0.005
Frequency of PCEA boluses	3 (1, 3)*	0 (0, 2)	0.5 (0, 2)	0 (0, 2)	<0.001

Data was shown as number (%), median (interquartile range).
*Adjusted $P < 0.05$, compared with dexmedetomidine groups. Hypotension was defined as a decrement > 20% from baseline blood pressure, or an absolute value < 90 mm Hg. Bradycardia was defined as heart rate < 50 bpm. Ru-Ying Pang: R-YP Yao-Hua Shen: Y-HS.

The exact mechanism of dexmedetomidine in reducing dose consumption of epidural local anesthetic remains unknown. It may exert its analgesic effect via the role of α2-AR adrenoceptors (2), via vasoconstriction (14), or through synergistic effects (15) with sodium channel blockers.

We chose fentanyl 2 μg/ml in this study because this concentration has been widely accepted clinically, and it has been well documented to reduce the dose requirement of epidural local anesthetic during labor analgesia (16). Moreover, epidural use of ropivacaine alone for labor analgesia would seem certain to necessitate an increase in its concentration, which would enhance lower limb motor block and reduce patient satisfaction. In fact, in the present study, the incidence of motor block in the 0.5 μg/ml of dexmedetomidine group was higher than in other lower-dose groups, implies that increasing doses of dexmedetomidine in the epidural solution could bring an increase in motor block. This perhaps explanation for this phenomenon may be due to a synergistic effect of dexmedetomidine with local anesthetics (15), through which dexmedetomidine not only enhanced the analgesic effect of local anesthesia, but also increased the side effect of motor block. However, this finding is the secondary outcome of this study, and the sample size may be not sufficient for this context and the possibility of statistical error cannot be excluded.

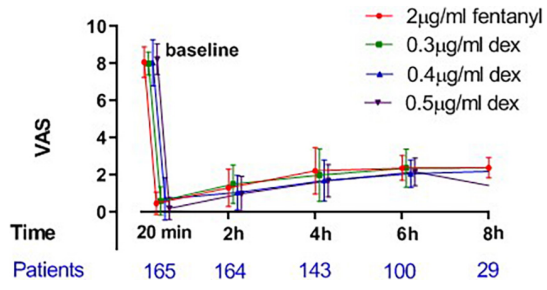

FIGURE 3
Mean VAS (0–10) ± SD over time during labor.

Of note, in a prior study but inconsistent with the results of our current study, we found that the use of epidural dexmedetomidine provided a dose-dependent reduction in the median effective concentration of ropivacaine for the induction of epidural labor analgesia (6). The explanation may be that using 0.125% of ropivacaine with 0.3 μg/ml dexmedetomidine for labor pain in conjunction with the PIEB plus PCEA protocol in both study designs may have caused patients to reach a plateau phase of relieving labor pain. If so, further increases in the dose of dexmedetomidine might only have resulted in non-therapeutic effects and even potentially increased risk of side effects such as a higher degree of motor block, as experienced in the 0.5 μg/ml dexmedetomidine group in the present study. Further study to determine the full dose-response of epidural ropivacaine with dexmedetomidine is warranted.

Although dexmedetomidine may be an important adjuvant alternative to opioids, especially in patients with extreme opioid sensitivity (vomiting and pruritus), the major disadvantage of this drug is the fact that it remains an investigational drug by the U.S. Food and Drug Administration for use in the epidural space. Similar to prior studies (6–8), our data showed no adverse effects of dexmedetomidine on maternal or neonatal outcomes. Human studies, as well as animal studies, have demonstrated the safety of using dexmedetomidine as a local adjuvant in peripheral, epidural, and intrathecal spaces without any neurological complications (17–19). Nevertheless, larger sample studies are warranted to further verify the safety of using dexmedetomidine as a neuraxial adjuvant.

There are limitations to the present study that need to be acknowledged. First, while the sample size was adequate to determine differences of our primary outcomes among the study groups, it was not powered sufficiently to definitively detect or reach conclusions on such aspects as side effects or other secondary outcomes. Second, due to the design of this study, the dose-response of dexmedetomidine on epidural ropivacaine was not clarified, and future studies on this topic may be of great interest. Third, although no additional adverse effects of dexmedetomidine were identified, there are no objective criteria for evaluating its neurological effects. Fourth, the objective of this study is to compare the mean amount of ropivacaine administered per hour among study groups, which was the primary outcome for which the study was powered. However, for the secondary outcomes, the sample size of the study may not be powered. Finally, patients experiencing "breakthrough pain" not rescued with a bolus of 10 ml of 0.25% ropivacaine plus 100 μg of fentanyl were excluded from the study, which could overestimate the effectiveness of the current analgesic strategy.

In conclusion, we found that epidural dexmedetomidine (0.3 and 0.4 μg/ml) is superior to epidural traditional fentanyl (2 μg/ml) in reducing hourly ropivacaine consumption and minimizing opioid-related side effects. Further large and multicenter studies are needed to validate adjuvant dexmedetomidine as an alternative to opioids before advising its routine clinical use.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Committee of Lin-Ping District Women and Children Care Hospital, Hangzhou, China. The patients/participants provided their written informed consent to participate in this study.

Author contributions

R-YP helped in designing and conducting the study, analyzing the data, and writing the manuscript. Y-HS, X-QJ, H-FX, YW, B-XZ, and S-FL helped in conducting the study and collecting the data. FX helped in the study design, data analysis, and manuscript preparation. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association between cervical length and massive intraoperative bleeding in patients with suspected placenta accreta spectrum combined with placenta previa: A retrospective cohort study

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Purpose: Abnormal placentation is a spectrum disorder that includes creta, increta, and percreta; the term placenta accreta spectrum (PAS) disorders is used as a broad term to describe all of these conditions. PAS can lead to life-threatening hemorrhage. The predictive value of cervical length (CL) in patients with PAS remains controversial. Thus, this study investigated the relationship between CL and the probability of major bleeding in patients with PAS and placenta previa.
Methods: This retrospective cohort study was conducted at a comprehensive tertiary hospital in Chongqing, China, between January 2018 and December 2020. The target independent and dependent variables were CL and intraoperative massive bleeding, respectively. The covariates included demographic, clinical, and ultrasound characteristics. Logistic regression was used to explore the association between CL and massive bleeding.
Results: In total, 317 participants were enrolled, in whom the prevalence of massive bleeding was 41.9% (133/317). The threshold of CL associated with massive bleeding (≥1,000 ml) was 33 mm based on a receiver operating characteristic curve. In the fully adjusted model for each additional unit of CL, the risk of massive bleeding decreased by 7% [95% confidence interval (CI), 0.88–0.98]. The risk of major bleeding was reduced by 44% in patients with a CL greater than 33 mm (95% CI, 0.33–0.97) compared with patients with a CL less than 33 mm.
Conclusions: CL was negatively associated with massive intraoperative bleeding in patients with PAS combined with placenta previa. When the CL was greater than 33 mm, the risk of bleeding decreased by 44%. Thus, CL can be used as a standalone parameter to identify the risk of massive intraoperative bleeding in patients with suspected PAS.

KEYWORDS

cervical length, massive bleeding, placenta accreta spectrum, placenta previa, cesarean section

Introduction

Abnormal placentation is a spectrum disorder that includes both abnormal adherence (placenta accreta) and abnormal invasion (placenta increta and placenta percreta); thus, the term placenta accreta spectrum (PAS) disorders is used here as a broad term to describe the condition in its entirety (1). The incidence of PAS has gradually increased with an increase in the rate of cesarean deliveries. Elective cesarean delivery remains the predominant treatment modality (2, 3). Intraoperative hemorrhage may lead to adverse obstetric outcomes during cesarean delivery in such patients.

PAS is one of the most commonly understood factors leading to massive hemorrhage (4). However, not all patients with PAS are at risk for major bleeding, and the risk may vary depending on the various forms of PAS. Although imaging is the best investigation method available for prenatal identification of invasive placentation, its sensitivity and specificity are not 100% (5). Some cases of placenta accreta are difficult to diagnose preoperatively, and the preoperative classification of PAS types remains challenging (6).

The ultrasound indicator cervical length (CL) can be easily obtained by transabdominal or vaginal ultrasound. Previous studies have demonstrated that CL can predict preterm labor and antepartum hemorrhage in patients with placenta previa and that a shorter CL is associated with antepartum hemorrhage (7, 8). A shorter CL in placenta previa was also linked to significant intraoperative blood loss, according to previous studies (9–11).

The predictive value of CL in patients with PAS remains controversial. Rac et al. concluded that in patients with placenta accreta, a shorter CL did not increase the likelihood of bleeding or preterm delivery (12). Although CL is associated with PAS, some studies have also indicated that it is not linked to the degree of placental implantation (13). Further research is needed to determine whether there is a link between CL and risk of intraoperative hemorrhage in patients with suspected PAS. In this context, this study aimed to investigate the relationship between CL and the likelihood of major bleeding in patients with PAS and placenta previa.

Materials and methods

Study design

This was a retrospective, cohort study. The target independent variable was CL, and the dependent variable was intraoperative massive bleeding. Intraoperative massive bleeding was defined as intraoperative bleeding ≥1,000 ml, and intraoperative bleeding <1,000 ml was considered as non-massive bleeding. Intraoperative blood loss was calculated using preoperative and postoperative hemoglobin values (14). Women with a calculated blood loss of ≥1,000 ml were included in the massive bleeding group, while those with a calculated bleeding volume of <1,000 ml were categorized into the non-massive bleeding group (15).

Study population

We reviewed the clinical data (extracted from the hospital electronic medical record system) of consecutive patients with PAS with placenta previa who underwent cesarean section (CS) between January 2018 and December 2020. The preoperative diagnosis of PAS was mainly based on the Placenta Accreta Spectrum Ultrasound Scoring System (PASUSS) and (16, 17) FIGO diagnostic criteria. From 2019, the diagnosis of PAS relied primarily on PASUSS. The need for obtaining informed consent was waived because of the retrospective nature of the study. This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. The inclusion criteria were patients with PAS with placenta previa, identified using color Doppler ultrasonography, and having no other prenatal disorders. The exclusion criteria were patients with additional obstetric diseases, a history of cervical cerclage and other cervical surgeries, and inadequate data.

Variables

CL was obtained through transabdominal ultrasound or transvaginal ultrasound, performed by an obstetric ultrasound specialized radiologist with 5 years of post-fellowship experience. The shortest value was determined as CL in the sagittal plane. The CL of the uterus was measured from the external os to the functional internal os. CL obtained from the last obstetric ultrasound before cesarean delivery was used as a reference. CL was generally measured on the day before surgery or the day of surgery. The accuracy of CL for identifying women at high risk of massive intraoperative hemorrhage was determined using receiver operating characteristic (ROC) curves. Other variables included (1) continuous variables: age, weight, height, placental thickness, gravidity, and gestational age; (2) categorical variables: curettage, hypervascularization (The degree of post-placental vascularization from visible to very strong is indicated by 1–4, respectively), previous CS, and history of hypertension and diabetes.

Treatment protocol

The standard procedure for hemorrhage prevention and bleeding control was followed during CS. The surgeon decided whether to perform an aortic balloon placement

before cesarean delivery, depending on the patient's condition. When possible, we developed a policy of prophylactic interruption of abdominal aortic balloon catheter placement, followed by placental separation and uterine preservation *via* cesarean delivery. Depending on the operative findings, the decision was made to remove the adherent placenta and apply local sutures in the placental bed or to leave the placenta in place and perform a hysterectomy after the newborn was delivered. The Triple-*P* procedure was used in some patients to preserve the uterus as much as possible.

Follow-up procedure

We performed the follow-up until the patient was discharged from the hospital. Follow-up data were stored in the hospital's electronic medical record system.

Statistical analysis

Continuous data are presented as the mean ± standard deviation or median values, depending on the normality of distribution. Normality was examined using the Shapiro–Wilk test. The t-test was used for continuous variables with a normal distribution. Categorical data are presented as the number of cases and corresponding percentage. Categorical and continuous data that did not show a normal distribution were analyzed using Pearson's chi-squared test, Fisher's exact test, or Mann–Whitney U test, as appropriate.

Univariate and multivariate binary logistic regression analyses were performed with four constructed models: Model 1, no covariates adjusted; Model 2, only adjusted for sociodemographic data; Model 3, adjusted for covariates presented in Table 1; and Model 4, adjusted for all variables in Model 2 + Model 3.

Stratified binary logistic regression models were used for subgroup analyses. We performed an interaction test after converting the continuous variables into categorical variables based on the clinical cut-off point. The likelihood ratio test was followed by tests for the effect modification of subgroup indicators. The purpose of converting CL into a categorical variable was to validate the results of CL as a continuous variable.

All the analyses were performed with the statistical software packages R 3.3.2 (http://www.R-project.org, The R Foundation) and Free Statistics software version 1.6. A two-tailed test was performed. *P* values less than 0.05 (two-sided) were considered statistically significant.

Results

A total of 317 participants were enrolled for the final data analysis (Figure 1 presents a flowchart of patient selection).

TABLE 1 Baseline characteristics of the study participants.

Variables	Total ($n = 317$)	CL < 33 ($n = 140$)	CL ≥ 33 ($n = 177$)	*p*
Age (year), Mean ± SD	32.9 ± 4.3	32.8 ± 4.4	33.0 ± 4.2	0.649
Weight (kg), Mean ± SD	68.4 ± 8.8	68.2 ± 8.9	68.6 ± 8.8	0.678
Height (cm), Mean ± SD	157.9 ± 4.8	157.9 ± 4.4	157.8 ± 5.2	0.860
Gestational age (week)	36.3 ± 1.6	36.2 ± 1.7	36.5 ± 1.5	0.116
Gravidity, Mean ± SD	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	4.0 (2.0, 5.0)	0.621
Curettage, *n* (%)	2.0 (1.0, 3.0)	1.0 (1.0, 2.0)	2.0 (1.0, 3.0)	0.179
Previous CS, *n* (%)				0.173
≤1	268 (84.5)	114 (81.4)	154 (87)	
≥2	49 (15.5)	26 (18.6)	23 (13)	
Hypervascularization, *n* (%)				<0.001
1	108 (34.1)	31 (22.1)	77 (43.5)	
2	119 (37.5)	59 (42.1)	60 (33.9)	
3	67 (21.1)	37 (26.4)	30 (16.9)	
4	23 (7.3)	13 (9.3)	10 (5.6)	
Placental thickness (mm), Mean ± SD	42.0 ± 9.0	43.6 ± 9.1	40.8 ± 8.8	0.006
Suspected PAS, *n* (%)				<0.001
No PAS	18 (5.7)	2 (1.4)	16 (9)	
Creta	103 (32.5)	29 (20.7)	74 (41.8)	
Increta	170 (53.6)	91 (65)	79 (44.6)	
Percreta	26 (8.2)	18 (12.9)	8 (4.5)	
Diabetes, *n* (%)	83 (26.2)	44 (31.4)	39 (22)	0.059
Hypertension, *n* (%)	11 (3.5)	3 (2.1)	8 (4.5)	0.358

CL, cervical canal length; CS, cesarean section; SD, standard deviation; PAS, placenta accreta spectrum.

The baseline characteristics of the selected participants are shown in Table 1, according to the optimal cut-off value based on the ROC of CL. Participants in the lower CL group had a greater volume of blood loss, longer operation and hospitalization time, and higher incidence of intra-abdominal balloon occlusion (IABO) and blood transfusion than those in the higher CL group (Table 2).

The results of univariate analyses are shown in Supplementary Table S1. Univariate binary logistic regression analysis revealed that age, height, and weight were not associated with massive intraoperative bleeding. We further discovered that CL was negatively associated with massive intraoperative bleeding. In contrast, univariate analysis showed that placental thickness, previous CS, hypervascularization, and curettage were positively correlated with massive intraoperative bleeding.

In this study, we constructed four models to analyze the independent effects of CL on massive intraoperative bleeding (univariate and multivariate binary logistic regression analyses). The effect sizes [odds ratios (OR)] and 95% confidence intervals (CI) are listed in Table 3. In the unadjusted model (Model 1), the model-based effect size

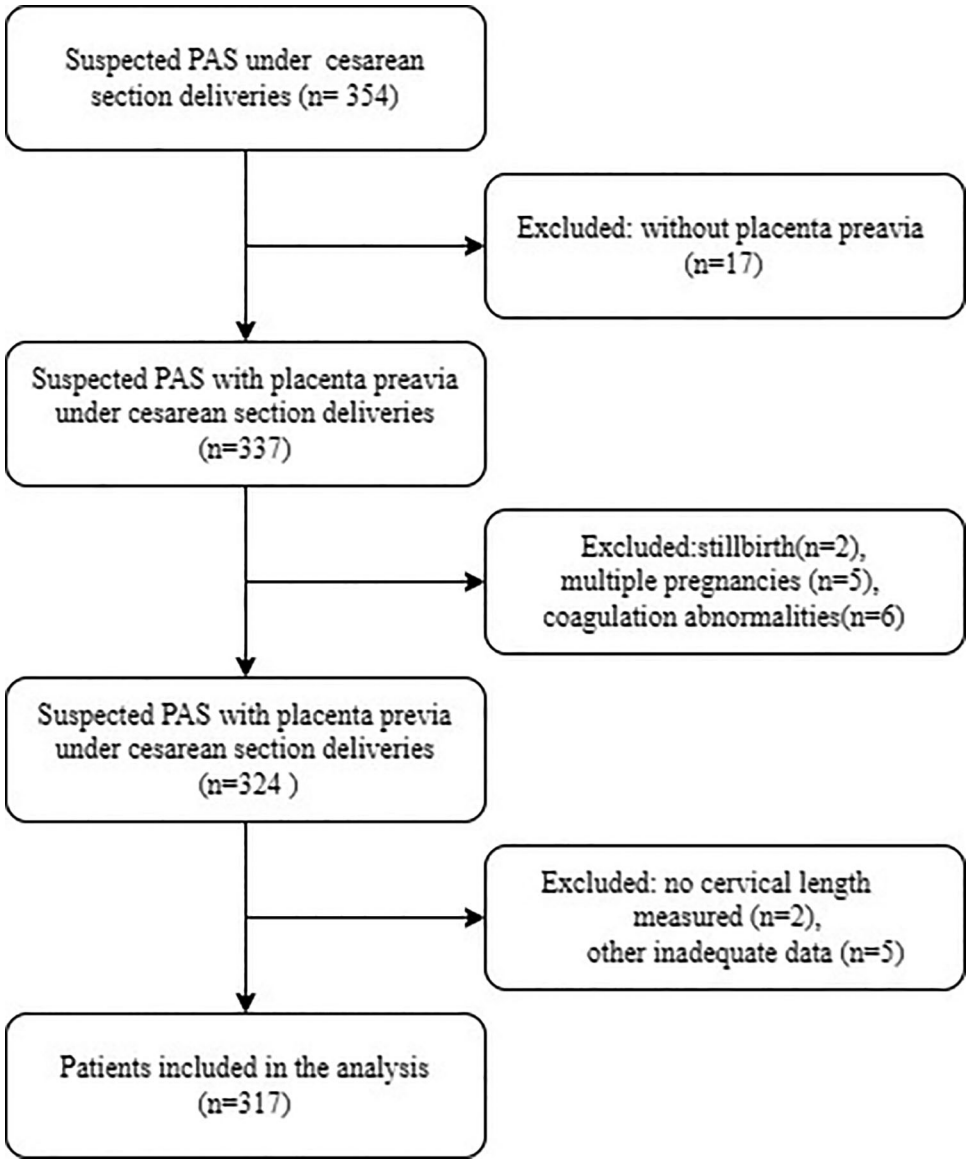

FIGURE 1
Flowchart showing the study population selection.

could be explained as the difference in one unit of CL associated with a 10% reduction in the risk of massive bleeding. In the minimum-adjusted model (Model 2), as the CL increased by one unit, the risk of massive bleeding decreased by 10% (95% CI, 0.86–0.95). In the fully adjusted model (Model 4), for each additional unit of CL, the risk of massive bleeding decreased by 7% (95% CI, 0.88–0.98). For sensitivity analysis, we converted the CL from a continuous variable to a categorical variable (optimal cut-off value based on ROC), and after adjusting for all variables, the risk of major bleeding was reduced by 44% in patients with a CL greater than 33 mm (95% CI, 0.33–0.97), compared with that in patients with a CL less than 33 mm.

We selected body weight, previous CS, history of diabetes, and incidence of IABO as stratification variables to study the trend of effect sizes for these variables (Figure 2); however, no significant interaction was observed ($P > 0.05$).

Discussion

Our findings indicated that CL was negatively associated with massive intraoperative bleeding after adjusting for other covariates. A shorter CL was associated with a higher risk of massive bleeding, independent of other ultrasound and clinical indicators. In addition, when the CL was greater than

TABLE 2 Intraoperative and postoperative data of the study participants.

Variables	Total ($n = 317$)	CL < 33 ($n = 140$)	CL ≥ 33 ($n = 177$)	p
Blood loss (mL), Median (IQR)	611.0 (436.0, 1124.0)	1002.0 (464.2, 1440.0)	566.0 (422.0, 1023.0)	0.003
IABO, *n* (%)	168 (53.0)	99 (70.7)	69 (39)	<0.001
Blood transfusion, *n* (%)	78 (24.6)	42 (30)	36 (20.3)	0.047
Postoperative transfusion, *n* (%)	60 (18.9)	36 (25.7)	24 (13.6)	0.006
Plasma, *n* (%)	55 (17.4)	31 (22.1)	24 (13.6)	0.045
Cryoprecipitate, *n* (%)	18 (5.6)	10 (7.1)	8 (4.6)	0.653
Autologous Blood Collection, *n* (%)	43 (13.6)	25 (17.9)	18 (10.2)	0.047
Uterine gauze stuffing, *n* (%)	45 (14.2)	25 (17.9)	20 (11.3)	0.097
Intrauterine balloon tamponade, *n* (%)	111 (35.0)	53 (37.9)	58 (32.8)	0.346
Uterine artery embolization, *n* (%)	25 (7.9)	14 (10)	11 (6.2)	0.214
Uterine Bondage, *n* (%)	141 (44.5)	67 (47.9)	74 (41.8)	0.282
Cervical lift suture, *n* (%)	226 (71.3)	108 (77.1)	118 (66.7)	0.041
Triple-*P* procedure, *n* (%)	58 (18.3)	29 (20.7)	29 (16.4)	0.322
Placenta left *in situ*, *n* (%)	21 (6.6)	12 (8.6)	9 (5.1)	0.215
Hysterectomy, *n* (%)	11 (3.5)	7 (5)	4 (2.3)	0.224
ICU admission, *n* (%)	12 (3.8)	5 (3.6)	7 (4)	0.859
Operation time (min), Median (IQR)	103.0 (85.0, 128.0)	111.5 (92.5, 142.2)	95.0 (80.0, 120.0)	< 0.001
Hospitalization time (day), Median (IQR)	6.0 (5.0, 7.0)	6.0 (5.0, 8.0)	5.0 (5.0, 7.0)	0.009
Neonatal weight (g), Mean ± SD	2880.9 ± 471.3	2823.3 ± 451.8	2926.5 ± 482.6	0.053
Neonatal Sex, *n* (%)				0.711
Male	169 (53.3)	73 (52.1)	96 (54.2)	
Female	148 (46.7)	67 (47.9)	81 (45.8)	

CL, cervical canal length; IABO, intra-abdominal balloon occlusion; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

TABLE 3 Multivariate analysis for massive bleeding.

Outcome	Non-adjusted Model		Model I		Model II		Model III	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Cervical length	0.9 (0.86–0.95)	<0.001	0.9 (0.86-0.95)	<0.001	0.93 (0.88~0.99)	0.016	0.93 (0.88~0.98)	0.011
Cervical length classification								
<33 mm	Reference		Reference		Reference		Reference	
≥33 mm	0.45 (0.28~0.7)	0.001	0.44 (0.28~0.7)	<0.001	0.55 (0.32~0.95)	0.032	0.56 (0.33~0.97)	0.039

Model I: Adjust for age, weight, and height.
Model II: Adjust for hypervascularization prior to CS, gravidity, gestational age, placental thickness, curettage, and IABO.
Model III: Adjusted for age, weight, height, hypervascularization, previous CS, gravidity, gestational age, placental thickness, curettage, and IABO.
OR, odds ratio; CI, confidence interval; CS, cesarean section; IABO, intra-abdominal balloon occlusion.

33 mm, the risk of bleeding decreased by 44% (95% CI, 0.33–0.97). Thus, CL could be used as a standalone parameter to aid in identifying the risk of massive intraoperative bleeding in patients with suspected PAS.

Similar findings have been reported in previous studies. In a previous study on patients with placenta previa, bleeding is negatively correlated with CL (8). As shown on the ROC curve, the threshold CL associated with major bleeding (>2500 ml) was 25 mm. The relative risk for massive bleeding in cases with a short CL (<25 mm) was 7.2 (95% CI, 2.3–22.3) in comparison to that in cases with a long CL (8). A short CL was also associated with poor maternal outcomes (18, 19). Fukushima et al. reported that in placenta previa, a CL ≤ 30 mm was associated with placental adhesions and massive intraoperative blood loss (9). A short cervix, especially shorter than 20.5 mm, may make the surgery more difficult and lead to increased bleeding (10). CL predicts surgical outcomes, and a shorter CL is associated with the need to perform a hysterectomy (11).

Most of the previous studies have focused on patients with placenta previa or hypoplacenta. Our findings support a similar

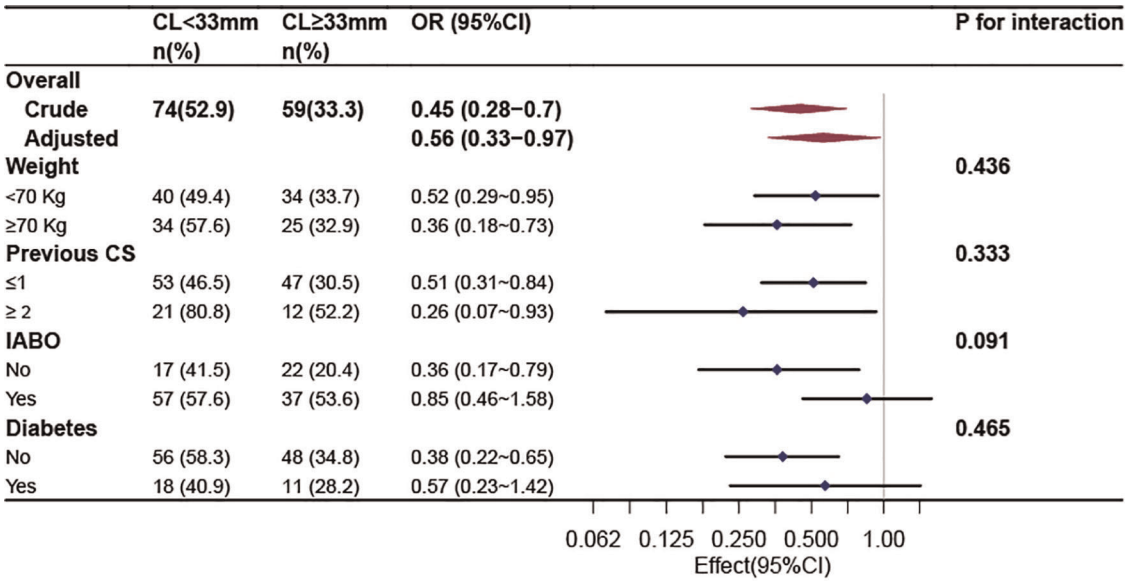

FIGURE 2
Stratified analyses of the association between cervical length and massive bleeding according to baseline characteristics.

relationship in patients with PAS. Although PAS is a risk factor for postpartum hemorrhage, our study found intraoperative hemorrhage in only a subset of patients, particularly after preoperative intervention or various intraoperative hemostatic measures. Furthermore, we confirmed a specific relationship between CL and intraoperative bleeding in patients with PAS. Using CL as a parameter, we were able to determine which patients with suspected PAS were more likely to have intraoperative hemorrhage.

Several hypotheses have been proposed to explain why people with short cervixes tend to bleed intraoperatively. First, most postpartum bleeding is caused by weak uterine contractions (20), which may be exacerbated in patients with a shortened cervix. Furthermore, a shorter cervix suggests that more cervical components are involved in the composition of the lower uterine segment, and fewer uterine muscles may affect lower uterine segment contraction, which is one of the reasons why these contractions are less intense (8, 21). When placental abruption occurs in the lower uterine segment, the muscle layer of this segment is unable to contract the torn blood vessels (22). Second, in patients with PAS combined with placenta previa, contraction of the lower uterine segment may be limited in the context of placental implantation (8). Third, shortening of the cervix makes surgical operations involving hemostasis more difficult and can prolong the time to hemostasis. A potentially effective method of controlling severe postpartum hemorrhage due to placenta previa/implanted placenta previa is turning the cervix into the uterine cavity and suturing the anterior and/or posterior cervical lips to the anterior and/or posterior wall of the lower uterine segment, respectively (23). In patients with focal placental implantation having a low fetal count and desiring future fertility, the use of the cervix as a tamponade combined with bilateral uterine artery ligation appears to be a safe alternative to hysterectomy (24). Fourth, patients with a shortened cervix have an increased probability of antepartum bleeding, which may deplete some clotting factors. As the time to hemostasis increases, excessive depletion of clotting factors can further increase the difficulty to achieve hemostasis, although this hypothesis needs to be confirmed by further studies. Fifth, a short cervix may present differences in placental blood supply compared to a long cervix, leading to increased difficulty in stopping bleeding and increased surgical difficulty (13).

This study has some limitations. First, some limitations inherent to its retrospective design, such as confounders and selection bias. Second, this was a retrospective study; therefore, CL was not measured prospectively. Instead, the CL measurements were obtained by transabdominal and transvaginal ultrasound, which may have affected the final result. The measurement of CL by different physicians may lead to biased results, although all of these physicians have extensive clinical experience and the CL obtained had good reproducibility, which should have limited the differences (25). Third, the CS procedure was performed by different surgeons with different choices or preferences, which may affect the final amount of intraoperative bleeding, even though all surgeons have the ultimate goal of stopping bleeding and protecting the uterus as much as possible. Fourth, all ultrasound-related metrics were obtained by reviewing the patients' ultrasound reports; therefore, some ultrasound

metrics could not be included in the reports. Consequently, some relevant indicators were excluded from the regression model. All of these indicators were potential confounding factors that could affect the final results.

In conclusion, CL is negatively associated with massive intraoperative bleeding in patients with PAS combined with placenta previa. This objective parameter will be easy to use even for non-expert imaging technicians for screening and will lead to an appropriate referral to centers of excellence for PAS disorders. When the CL was greater than 33 mm, the risk of bleeding decreased by 44% (95% CI, 0.33–0.97). Thus, CL can be used as a standalone parameter to aid in identifying the risk of massive intraoperative bleeding in women with suspected PAS.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the First Affiliated Hospital of Chongqing Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

FH: participated in the design of the study, collected the data and conducted the analysis, and drafted the manuscript. JW: designed the study and revised the manuscript. JZ, WW, YX, JW, and QL: collected the data. QJ and XY: carried out data analysis. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.1028494/full#supplementary-material.

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Dynamic risk prediction models for different subtypes of hypertensive disorders in pregnancy

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Background: Hypertensive disorders in pregnancy (HDP) are diseases that coexist with pregnancy and hypertension. The pathogenesis of this disease is complex, and different physiological and pathological states can develop different subtypes of HDP.
Objective: To investigate the predictive effects of different variable selection and modeling methods on four HDP subtypes: gestational hypertension, early-onset preeclampsia, late-onset preeclampsia, and chronic hypertension complicated with preeclampsia.
Methods: This research was a retrospective study of pregnant women who attended antenatal care and labored at Beijing Maternity Hospital, Beijing Haidian District Maternal and Child Health Hospital, and Peking University People's Hospital. We extracted maternal demographic data and clinical characteristics for risk factor analysis and included gestational week as a parameter in this study. Finally, we developed a dynamic prediction model for HDP subtypes by nonlinear regression, support vector machine, stepwise regression, and Lasso regression methods.
Results: The AUCs of the Lasso regression dynamic prediction model for each subtype were 0.910, 0.962, 0.859, and 0.955, respectively. The AUC of the Lasso regression dynamic prediction model was higher than those of the other three prediction models. The accuracy of the Lasso regression dynamic prediction model was above 85%, and the highest was close to 92%. For the four subgroups, the Lasso regression dynamic prediction model had the best comprehensive performance in clinical application. The placental growth factor was tested significant ($P < 0.05$) only in the stepwise regression dynamic prediction model for early-onset preeclampsia.
Conclusion: The Lasso regression dynamic prediction model could accurately predict the risk of four HDP subtypes, which provided the appropriate guidance and basis for targeted prevention of adverse outcomes and improved clinical care.

KEYWORDS

hypertensive disorders in pregnancy, subtype, risk factor analysis, modeling method, dynamic prediction model, lasso regression

Introduction

Hypertensive disorders in pregnancy (HDP) are diseases that coexist with pregnancy and hypertension, which are major causes of increased maternal morbidity and mortality (1–3). HDP includes gestational hypertension, preeclampsia, eclampsia, chronic hypertension complicated with preeclampsia, and gestational combined chronic hypertension (4, 5). PE can be divided into two subtypes according to the time of onset: early-onset preeclampsia and late-onset preeclampsia (6, 7). HDP can be predicted by relevant risk factors, leading to early treatment (8–11).

The pathogenesis of HDP is complex. Risk factors for HDP are related to clinical epidemiological factors (12, 13), hemodynamic factors (14, 15), basic biochemical factors (16), and biomarkers (17, 18). For vascular biomarkers, numerous studies confirmed that placental growth factor (PlGF) had the function of regulating placental trophoblast and endothelial cells, and had a good predictive value for preeclampsia (19–21). HDP has multiple risk factors, which cannot be accurately predicted by a single factor and requires a combined assessment of multiple risk factors (22, 23). To improve the accuracy of prediction, researchers carried out a variety of combinations of different risk factors. Stepan et al. (24) found that a combination of ultrasound, mean arterial pressure, clinical features, and PlGF improved the prediction of preeclampsia in the first trimester of pregnancy. Chen et al. (25) found that the combination of mean arterial pressure, PlGF, and pregnancy-associated plasma protein A was far superior to a single factor. Current studies on the prediction of HDP focused on static studies at specific gestational weeks (26, 27), while pregnancy is a dynamic process and various physiological factors are constantly changing during pregnancy (28). Therefore, it is necessary to conduct a continuous dynamic study of HDP.

Different HDP subtypes are based on different physiological and pathological conditions of pregnant women, and a single modeling approach is not effective in predicting HDP subtypes. Poon et al. (29) found that the early-onset preeclampsia prediction model had a high detection rate of 93.1% for early-onset preeclampsia, but only 35.7% and 18.3% for late-onset preeclampsia and gestational hypertension. Sun et al. (30) compared the prediction effects of different methods on HDP and found that the Lasso regression method had the best prediction effect.

In this paper, we integrated multiple risk factors and multiple modeling approaches to develop dynamic prediction models for HDP subtypes. The prediction effects of various models were compared to select the optimal prediction model for effective prediction of each subtype.

Materials and methods

Research object

We performed a retrospective study on pregnant women who attended antenatal checkups at Beijing Maternity Hospital from 2006 to 2008, at Beijing Haidian District Maternal and Child Health Hospital from 2015 to 2016, and at Peking University People's Hospital from July 2015 to 2017. Our control group was healthy pregnant women without hypertensive disorders during pregnancy, not taking long-term medication, and without fetal malformations. A total of 1,267 women were

TABLE 1 Subgroups of the studied population.

Group	Number of people
GH	205
EOPE	95
LOPE	234
CHCP	85
Control	648

GH, gestational hypertension; EOPE, early-onset preeclampsia; LOPE, late-onset preeclampsia; CHCP, chronic hypertension complicated with preeclampsia; Control, normal pregnancy women.

TABLE 3 Dynamic factors.

Type	Factors
Clinical epidemiologic factors	BMI
Hemodynamic factors	SBP, DBP, PP, MAP, K, CO, CI, TPR
Blood biochemical factors	HCT, MPV, PLT, ALT, AST, CRE, UA
Biomarkers	PlGF

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; K, pulse wave shape coefficient; CO, cardiac output; CI, cardiac index; TPR, total peripheral resistance; HCT, hematocrit; MPV, mean platelet volume; PLT, platelet count; ALT, aspartame aminotransferase; AST, alanine aminotransferase; CRE, creatinine; UA, uric acid; PlGF, placental growth factor.

TABLE 2 Static factors.

Type	Factors
Quantitative factors	Age, height, pre-BMI
Qualitative factors	First birth, multiple pregnancy, history of spontaneous abortion, history of HDP, history of diabetes, family history of hypertension, family history of diabetes, gestational diabetes, pregestational diabetes mellitus, pregnancy combined with immune system disorders, pregnancy combined with hematologic disorders, pregnancy combined with thyroid disorders

Pre-BMI, pre-pregnancy body mass index.

TABLE 4 Static factors analysis of gestational hypertension.

Factor	GH	Control	OR
Qualitative factors			
First birth	145 (76.3%)	515 (81.4%)	0.738
Multiple pregnancy	5 (2.6%)*	4 (0.6%)	4.250
History of spontaneous abortion	47 (24.7%)	141 (22.3%)	1.147
History of HDP	1 (0.5%)	1 (0.2%)	3.344
History of diabetes	5 (2.6%)	10 (1.6%)	1.684
Family history of hypertension	41 (21.6%)	105 (16.6%)	1.384
Family history of diabetes	8 (4.2%)	32 (5.1%)	0.826
Gestational diabetes	21 (11.1%)*	37 (5.8%)	2.002
Pregestational diabetes mellitus	5 (2.6%)*	2 (0.3%)	8.527
Immune system disorders in pregnancy	4 (2.1%)	14 (2.2%)	0.951
Hematologic disorders in pregnancy	4 (2.1%)	20 (3.2%)	0.659
Thyroid disease in pregnancy	14 (7.4%)	30 (4.7%)	1.599
Quantitative factors			
Age (years)	30.830 ± 3.908[a]	30.220 ± 3.742[a]	–
Height (m)	1.626 ± 0.049[a]	1.624 ± 0.048[a]	–
Pre-BIM (kg/m^2)	23.926 ± 4.503[a,**]	21.140 ± 3.101[a]	–

GH, gestational hypertension; Control, normal pregnancy women; Pre-BMI, pre-pregnancy body mass index.
[a]Mean and standard deviation.
*$P < 0.05$ compared to Control.
**$P < 0.05$ compared to Control.

TABLE 5 Static factors analysis of early-onset preeclampsia.

Factor	EOPE	Control	OR
Qualitative factors			
First birth	56 (70.0%)	515 (81.4%)	0.535
Multiple pregnancy	7 (8.8%)**	4 (0.6%)	15.079
History of spontaneous abortion	39 (48.8%)**	141 (22.3%)	3.319
History of HDP	2 (2.5%)*	1 (0.2%)	16.205
History of diabetes	2 (2.5%)	10 (1.6%)	1.597
Family history of hypertension	15 (18.8%)	105 (16.6%)	1.160
Family history of diabetes	2 (2.5%)	32 (5.1%)	0.482
Gestational diabetes	2 (2.5%)	37 (5.8%)	0.413
Pregestational diabetes mellitus	0	2 (0.3%)	0.997
Immune system disorders in pregnancy	2 (2.5%)	14 (2.2%)	1.134
Hematologic disorders in pregnancy	2 (2.5%)	20 (3.2%)	0.786
Thyroid disease in pregnancy	2 (2.5%)	30 (4.7%)	0.515
Quantitative factors			
Age (years)	30.650 ± 4.543[a]	30.220 ± 3.742[a]	–
Height (m)	1.618 ± 0.051[a]	1.624 ± 0.048[a]	–
Pre-BIM (kg/m^2)	55.734 ± 8.588[a,**]	21.140 ± 3.101[a]	–

EOPE, early-onset preeclampsia; control, normal pregnancy women; Pre-BMI, pre-pregnancy body mass index.
[a]Mean and standard deviation.
*$P < 0.05$ compared to Control.
**$P < 0.05$ compared to Control.

TABLE 6 Static factors analysis of late-onset preeclampsia.

Factor	LOPE	Control	OR
Qualitative factors			
First birth	172 (78.5%)	515 (81.4%)	0.839
Multiple pregnancy	12 (5.5%)**	4 (0.6%)	9.116
History of spontaneous abortion	90 (41.1%)**	141 (22.3%)	2.434
History of HDP	6 (2.7%)**	1 (0.2%)	17.803
History of diabetes	7 (3.2%)	10 (1.6%)	2.057
Family history of hypertension	51 (23.3%)*	105 (16.6%)	1.527
Family history of diabetes	24 (11.0%)*	32 (5.1%)	2.312
Gestational diabetes	12 (5.5%)	37 (5.8%)	0.934
Pregestational diabetes mellitus	1 (0.5%)	2 (0.3%)	1.447
Immune system disorders in pregnancy	9 (4.1%)	14 (2.2%)	1.895
Hematologic disorders in pregnancy	2 (0.9%)	20 (3.2%)	0.282
Thyroid disease in pregnancy	8 (3.7%)	30 (4.7%)	0.762
Quantitative factors			
Age (years)	30.350 ± 4.300[a]	30.220 ± 3.742[a]	–
Height (m)	1.619 ± 0.053[a]	1.624 ± 0.048[a]	–
Pre-BIM (kg/m^2)	23.239 ± 3.916[a,**]	21.140 ± 3.101[a]	–

LOPE, late-onset preeclampsia; Control, normal pregnancy women; Pre-BMI, pre-pregnancy body mass index.
[a]Mean and standard deviation.
*$P < 0.05$ compared to Control.
**$P < 0.05$ compared to Control.

included in this study, and they were divided into four HDP subgroups and a normal pregnancy group (Table 1).

Factors included in the analysis

The following data were collected from the maternal electronic medical records of the hospital: (1) the demographic data of pregnant women; (2) the clinical examination index. We classified the collected factors according to whether they changed with pregnancy: (a) static factors; (b) dynamic factors.

Static factors

Static factors were divided into two categories (Table 2): (i) quantitative factors, included age, height, and pre-pregnancy body mass index; (ii) qualitative factors, included first birth, multiple pregnancy, maternal history of disease, maternal family history of disease and maternal complications.

Dynamic factors

Dynamic factors were divided into four categories (Table 3): (i) clinical epidemiologic factors; (ii) hemodynamic factors; (iii) basic biochemical factors; (iiii) biomarkers.

TABLE 7 Static factors analysis of chronic hypertension complicated with preeclampsia.

Factors	CHCP	Control	OR
Qualitative factors			
First birth	52 (74.3%)	515 (81.4%)	0.662
Multiple pregnancy	3 (4.3%)*	4 (0.6%)	7.041
History of spontaneous abortion	11 (15.7%)	141 (22.3%)	0.651
History of HDP	1 (1.4%)	1 (0.2%)	9.159
History of diabetes	0	10 (1.6%)	0.984
Family history of hypertension	21 (30.0%)*	105 (16.6%)	2.155
Family history of diabetes	3 (4.3%)	32 (5.1%)	0.841
Gestational diabetes	11 (15.7%)*	37 (5.8%)	3.003
Pregestational diabetes mellitus	6 (8.6%)**	2 (0.3%)	29.578
Immune system disorders in pregnancy	7 (10.0%)**	14 (2.2%)	4.913
Hematologic disorders in pregnancy	1 (1.4%)	20 (3.2%)	0.444
Thyroid disease in pregnancy	8 (11.4%)*	30 (4.7%)	2.594
Quantitative factors			
Age (years)	31.930 ± 5.123[a,*]	30.220 ± 3.742[a]	–
Height (m)	1.629 ± 0.055[a]	1.624 ± 0.048[a]	–
Pre-BIM (kg/m^2)	24.142 ± 5.157[a,**]	21.140 ± 3.101[a]	–

CHCP, chronic hypertension complicated with preeclampsia; Control, normal pregnancy women; Pre-BMI, pre-pregnancy body mass index.
[a]Mean and standard deviation.
*$P < 0.05$ compared to Control.
**$P < 0.01$ compared to Control.

Dynamic prediction model

In this paper, the data were characterized by a large variety of parameters and the data volume was a small sample (in thousands), so we chose nonlinear regression, support vector machine (SVM), stepwise regression and Lasso regression to develop the prediction models. The advantages of these methods were that they were suitable for small samples and had good generalization ability. Among these methods, stepwise regression and Lasso regression had the function of automatic filtering variables.

Dynamic factors changed continuously during pregnancy, so we included the gestational week as a parameter in this research from both the formula and algorithm perspectives: we constructed a custom regression dynamic gestational week fitting formula by using nonlinear regression; we developed dynamic prediction models by using SVM, stepwise regression and Lasso regression. In model training for each subgroup, we selected 15 pregnant women in the subgroup and control group to form the validation set, and the rest pregnant women were divided into training set and test set at a ratio of 7:3.

TABLE 8 Dynamic factors analysis of gestational hypertension.

Factor	Group	10–13 weeks	14–20 weeks	21–27 weeks	28–34 weeks	35–40 weeks
SBP (mmHg)	GH	122.450*	120.556*	122.513*	125.667*	128.714*
	Control	115.581	111.809	109.199	110.033	109.543
DBP (mmHg)	GH	80.150*	77.917*	78.897*	79.190*	82.286*
	Control	73.806	69.953	68.460	69.510	69.139
PP (mmHg)	GH	42.300	42.639	43.615*	46.476*	46.429*
	Control	41.775	41.856	40.738	40.523	40.404
MAP (mmHg)	GH	95.544*	92.776*	95.436*	96.776*	100.645*
	Control	90.372	85.705	83.575	84.479	85.083
K	GH	0.375*	0.361*	0.386	0.379	0.398
	Control	0.402[#]	0.381	0.375	0.373	0.396
CO (L/min)	GH	4.824*	4.987*	4.783	5.475*	5.038*
	Control	4.316	4.784	4.871	4.967	4.493
CI [L/(min m^2)]	GH	3.015	3.168*	2.884	3.147	2.867
	Control	2.778	3.043	3.006	3.000	2.633
TPR (mmHg s/ml)	GH	1.203[#]	1.077*	1.294[#]	1.096	1.267[#]
	Control	1.332[#]	1.139	1.090	1.080	1.231[#]
HCT (%)	GH	37.415	37.422*	36.793*	37.505*	37.368
	Control	37.599	35.222	35.183	36.119	36.509
MPV (fl)	GH	9.578*	10.686*	9.839	9.571	9.671
	Control	8.974	9.254	9.624	9.666	9.415
PLT (×10^9/L)	GH	211.523	223.564	224.368*	198.786	202.536
	Control	223.024	220.193	205.692	196.365	196.159
ALT (U/L)	GH	17.162*	16.001*	20.319*	22.716	23.054
	Control	23.891	21.525	22.736	21.809	22.921
AST (U/L)	GH	20.096*	18.537*	21.190*	23.286	23.714
	Control	23.752	22.655	23.204	22.731	23.656
CRE (μmol/L)	GH	47.295*	52.869*	64.183	63.336*	55.543
	Control	52.284	61.909	65.824	49.658	55.100
UA (μmol/L)	GH	206.329	235.840*	245.833	282.490*	301.645*
	Control	200.676	240.863	246.089	228.416	265.853

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; K, pulse wave shape coefficient, dimensionless; CO, cardiac output; CI, cardiac index; TPR, total peripheral resistance; HCT, hematocrit; MPV, mean platelet volume; PLT, platelet count; ALT, aspartame aminotransferase; AST, alanine aminotransferase; CRE, creatinine; UA, uric acid.
*$P < 0.05$ compared to Control.
[#]Value outside the normal range.

Statistical analysis

Quantitative factors are presented as X (mean) ± SD (standard deviation). Qualitative factors are presented as percentages (%). Risk factors were screened for each HDP subgroup. For static factors, we conducted independent sample T test for quantitative factors and selected factors with $P < 0.05$; we performed chi-square test for qualitative factors, and selected factors with OR > 1 and $P < 0.05$. For dynamic factors, the clinical epidemiological factors and biomarkers for this research were body mass index and PlGF. A large number of researches had confirmed that body mass index and PlGF were risk factors for HDP (31, 32), so we analyzed

TABLE 9 Dynamic factors analysis of early-onset preeclampsia.

Factor	Group	10–13 weeks	14–20 weeks	21–27 weeks	28–34 weeks	35–40 weeks
SBP (mmHg)	EOPE	114.438	124.286*	120.000*	118.385*	148.963*,#
	Control	115.547	112.313	109.252	108.252	110.013
DBP (mmHg)	EOPE	75.438	77.857*	77.316*	75.538*	96.074*,#
	Control	73.795	70.270	68.454	68.034	69.479
PP (mmHg)	EOPE	39.000	46.429	42.684	42.846	52.889*,#
	Control	41.752	42.043	40.797	40.218	40.534
MAP (mmHg)	EOPE	91.553	95.680*	93.128*	91.603*	117.952*
	Control	90.336	86.029	83.583	84.195	84.453
K	EOPE	0.414#	0.387	0.373	0.385*	0.415*,#
	Control	0.401#	0.380	0.375	0.373	0.403#
CO (L/min)	EOPE	4.071	5.286	5.181	5.215	5.273*
	Control	4.320	4.795	4.876	4.969	4.302
CI [L/(min m^2)]	EOPE	2.573	3.088	3.203	3.174	2.960*
	Control	2.781	3.048	3.006	3.000	2.547
TPR (mmHg s/ml)	EOPE	1.494#	1.121#	1.112	1.410*,#	1.105
	Control	1.331#	1.136#	1.088	1.079	1.267#
HCT (%)	EOPE	37.321	38.512*	38.329*	35.985	37.654
	Control	37.591	35.246	35.197	36.129	36.175
MPV (fl)	EOPE	8.902	9.106	9.692	9.678	10.477*
	Control	8.986	9.277	9.615	9.664	9.203
PLT (×10^9/L)	EOPE	228.482	241.275	192.046	180.378	180.923
	Control	222.409	221.554	205.166	196.200	199.134
ALT (U/L)	EOPE	19.669	20.446	21.886	23.333*	23.500
	Control	23.786	21.423	22.692	21.814	22.765
AST (U/L)	EOPE	21.206	21.964	22.694	23.889*	24.000
	Control	23.710	22.497	23.175	22.735	23.563
CRE (μmol/L)	EOPE	47.761	62.517	62.098	76.275*	56.395
	Control	52.227	61.248	65.818	49.743	54.863
UA (μmol/L)	EOPE	212.681	231.447	232.684*	335.053*	276.247
	Control	200.542	240.577	246.082	228.289	263.255

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; K, pulse wave shape coefficient, dimensionless; CO, cardiac output; CI, cardiac index; TPR, total peripheral resistance; HCT, hematocrit; MPV, mean platelet volume; PLT, platelet count; ALT, aspartame aminotransferase; AST, alanine aminotransferase; CRE, creatinine; UA, uric acid.
*$P < 0.05$ compared to Control.
#Value outside the normal range.

TABLE 10 Dynamic factors analysis of late-onset preeclampsia.

Factor	Group	10–13 weeks	14–20 weeks	21–27 weeks	28–34 weeks	35–40 weeks
SBP (mmHg)	LOPE	114.118	120.226*	120.039*	127.897*	136.083*
	Control	115.575	112.009	109.117	110.067	109.280
DBP (mmHg)	LOPE	73.647	76.547*	74.471*	80.971*	90.861*,#
	Control	73.856	70.164	68.400	69.537	68.986
PP (mmHg)	LOPE	40.471	43.679	45.569*	46.926*	45.222*
	Control	41.719	41.845	40.717	40.530	40.294
MAP (mmHg)	LOPE	90.119	92.526*	91.526*	98.891*	108.468*
	Control	90.369	85.847	83.510	84.510	84.928
K	LOPE	0.407#	0.374	0.379	0.383*	0.387
	Control	0.401#	0.380	0.375	0.373	0.397
CO (L/min)	LOPE	4.313	4.900	5.248	5.424*	5.206*
	Control	4.322	4.796	4.867	4.968	4.458
CI [L/(min m^2)]	LOPE	2.774	3.183	3.195	3.201*	2.927*
	Control	2.782	3.055	3.005	3.003	2.627
TPR (mmHg s/ml)	LOPE	1.347#	1.149	1.118	1.152	1.339#
	Control	1.331#	1.134	1.090	1.080	1.238#
HCT (%)	LOPE	37.584	36.492*	36.633*	36.976	36.972
	Control	37.588	35.196	35.173	36.079	36.586
MPV (fl)	LOPE	8.943	9.710*	9.403	9.791	10.297*
	Control	8.987	9.285	9.600	9.660	9.411
PLT (×10^9/L)	LOPE	223.983	201.779*	203.542	193.047	179.028
	Control	222.049	220.816	205.503	195.800	194.364
ALT (U/L)	LOPE	19.394	18.746*	22.673	22.334	23.500
	Control	23.788	21.506	22.769	21.834	22.888
AST (U/L)	LOPE	20.782	19.882*	22.845	23.326	24.000
	Control	23.708	22.572	23.215	22.754	23.636
CRE (μmol/L)	LOPE	48.396	53.677*	65.454	65.037*	61.924*
	Control	52.211	61.427	65.848	49.630	55.067
UA (μmol/L)	LOPE	203.576	211.578*	238.838*	304.248*	308.173*
	Control	200.624	240.662	246.135	228.304	265.950

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; K, pulse wave shape coefficient, dimensionless; CO, cardiac output; CI, cardiac index; TPR, total peripheral resistance; HCT, hematocrit; MPV, mean platelet volume; PLT, platelet count; ALT, aspartame aminotransferase; AST, alanine aminotransferase; CRE, creatinine; UA, uric acid.
*$P < 0.05$ compared to Control.
#Value outside the normal range.

the hemodynamic and basic biochemical factors. We divided the pregnant woman's gestational weeks into five stages: 0–13, 14–20, 21–28, 29–34, 35–40 weeks. We performed independent sample *t*-tests for hemodynamic and basic biochemical factors at each stage, and selected factors with $P < 0.05$ and abnormal value (mean value outside the normal range).

We used IBM SPSS Statistics 26.0 to develop a custom dynamic gestational week fitting formula. Matlab 2019b was used for SVM model research. R software (v4.0.1) was used for stepwise regression and Lasso regression model researches. We compared model prediction effects by area under the ROC curve (AUC), accuracy, and the model was externally validated by the validation set.

Results

Analysis of static risk factors

For gestational hypertension, we compared qualitative factors between the gestational hypertension group and the control group, and found there were statistically significant differences in multiple pregnancy, gestational diabetes and pregestational diabetes mellitus between the two groups (OR > 1 and $P < 0.05$). The pre-pregnancy body mass index of gestational hypertension group was significantly higher than that of control group ($P < 0.05$) (Table 4). For early-onset preeclampsia, the qualitative factors that met OR > 1 and $P < 0.05$ were multiple pregnancy, history of spontaneous abortion and history of HDP. The

TABLE 11 Dynamic factors analysis of chronic hypertension complicated with preeclampsia.

Factors	Group	10–13 weeks	14–20 weeks	21–27 weeks	28–34 weeks	35–40 weeks
SBP (mmHg)	LOPE	125.429*	130.750*	136.091*	136.121*	136.167*
	Control	115.547	112.215	109.366	110.162	112.211
DBP (mmHg)	LOPE	81.810*	87.500*	92.455*,#	92.467*,#	92.533*,#
	Control	73.795	70.256	68.201	69.595	70.566
PP (mmHg)	LOPE	43.619	43.250	43.636	42.133	44.833
	Control	41.752	41.959	41.166	40.566	41.645
MAP (mmHg)	LOPE	96.579*	101.917*	107.244*	95.182*	108.871
	Control	90.336	86.109	83.496	84.582	87.043
K	LOPE	0.354*	0.350*	0.356*	0.370	0.392
	Control	0.401#	0.383	0.375	0.373	0.397
CO (L/min)	LOPE	4.981*	5.000*	4.817	5.044	4.951
	Control	4.320	4.746	4.908	4.981	4.627
CI [L/(min m^2)]	LOPE	3.237*	3.250*	3.115	3.072	2.870
	Control	2.781	3.021	3.025	3.001	2.691
TPR (mmHg s/ml)	LOPE	1.068*	1.050*	1.121	1.173	1.342#
	Control	1.331#	1.151	1.081	1.077	1.224#
HCT (%)	LOPE	35.617*	37.124*	37.442*	37.173	38.767
	Control	37.585	35.258	35.206	36.317	36.343
MPV (fl)	LOPE	10.066*	11.312*	11.054*	10.600*	10.750*
	Control	8.986	9.226	9.596	9.725	9.523
PLT ($\times 10^9$/L)	LOPE	195.799*	247.307	221.002	210.400	192.667
	Control	222.409	223.213	204.596	195.338	195.494
ALT (U/L)	LOPE	14.901*	28.181*	22.676	19.767	22.652
	Control	23.786	21.579	22.735	21.916	23.170
AST (U/L)	LOPE	24.147	50.114*,#	22.457	21.333	22.409
	Control	23.710	22.604	23.227	22.798	23.804
CRE (μmol/L)	LOPE	44.370*	59.639	52.385*	63.622*	62.585*
	Control	52.227	61.668	66.185	49.830	55.701
UA (μmol/L)	LOPE	220.557*	321.105*	252.957	302.115*	344.232*
	Control	200.542	240.701	246.347	228.714	264.888

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; K, pulse wave shape coefficient, dimensionless; CO, cardiac output; CI, cardiac index; TPR, total peripheral resistance; HCT, hematocrit; MPV, mean platelet volume; PLT, platelet count; ALT, aspartame aminotransferase; AST, alanine aminotransferase; CRE, creatinine; UA, uric acid.
*$P < 0.05$ compared to Control.
#Value outside the normal range.

quantitative factors that met $P < 0.05$ was pre-pregnancy body mass index (Table 5). For late-onset preeclampsia, we found significant differences between the late-onset preeclampsia group and control group in multiple pregnancy, history of spontaneous abortion, history of HDP, family history of hypertension and family history of diabetes (OR > 1 and $P < 0.05$). The quantitative factors that were significantly different between the two groups was pre-pregnancy body mass index ($P < 0.05$) (Table 6). For chronic hypertension complicated with preeclampsia, qualitative factors of multiple pregnancy, family history of hypertension, gestational diabetes, pregestational diabetes mellitus, pregnancy combined with immune system disorders and pregnancy combined with thyroid disorders were risk factors of chronic hypertension complicated with preeclampsia (OR > 1 and $P < 0.05$). Pre-pregnancy body mass index among the quantitative factors was a risk factor for chronic hypertension combined with preeclampsia ($P < 0.05$) (Table 7).

Analysis of dynamic risk factors

We analyzed all dynamic factors within the five gestational stages, and found dynamic factors were significantly different between the gestational hypertension group and the control group (Table 8). The difference in platelet count (PLT) between the early-onset preeclampsia group and the control group was not statistically significant, and the mean value did not exceed the normal range (Table 9). In this paper, we did not consider PLT as a risk factor for early-onset preeclampsia. We found there was no statistically significant differences in total peripheral resistance (TPR) between the late-onset preeclampsia group and the control group, but the TPR was outside the normal range at 10–13 and 35–40 weeks (Table 10). Therefore, we considered TPR as a risk factor for late-onset preeclampsia. The difference in pulse pressure (PP) between the chronic hypertension combined with preeclampsia group and the control group was not statistically significant, and the mean value did not exceed the normal range (Table 11). Therefore, we did not consider PP as a risk factor for chronic hypertension combined with preeclampsia.

Model construction results

We used nonlinear regression, SVM, step regression and Lasso regression for each HDP subgroup to develop prediction models. The *P*-values of the models were all less than 0.001, which indicated that the models were stable. We compared the prediction results of the four models, the Lasso regression prediction model of the gestational hypertension was optimal: accuracy = 90.32%, AUC = 0.910, sensitivity = 75.86%, specificity = 93.32%; the Lasso regression prediction model of the early-onset preeclampsia was optimal: accuracy = 91.78%, AUC = 0.962, sensitivity = 86.21%, specificity = 92.18%; Lasso regression prediction model for late-onset preeclampsia was optimal: accuracy = 85.58%, AUC = 0.859, sensitivity = 72.73%, specificity = 89.47%; Lasso regression prediction model for chronic hypertension complicated with preeclampsia was optimal: accuracy = 91.72%, AUC = 0.955, sensitivity = 93.10%, specificity = 91.63% (Figure 1 and Table 12). PlGF was tested significant ($P < 0.05$) only in the stepwise

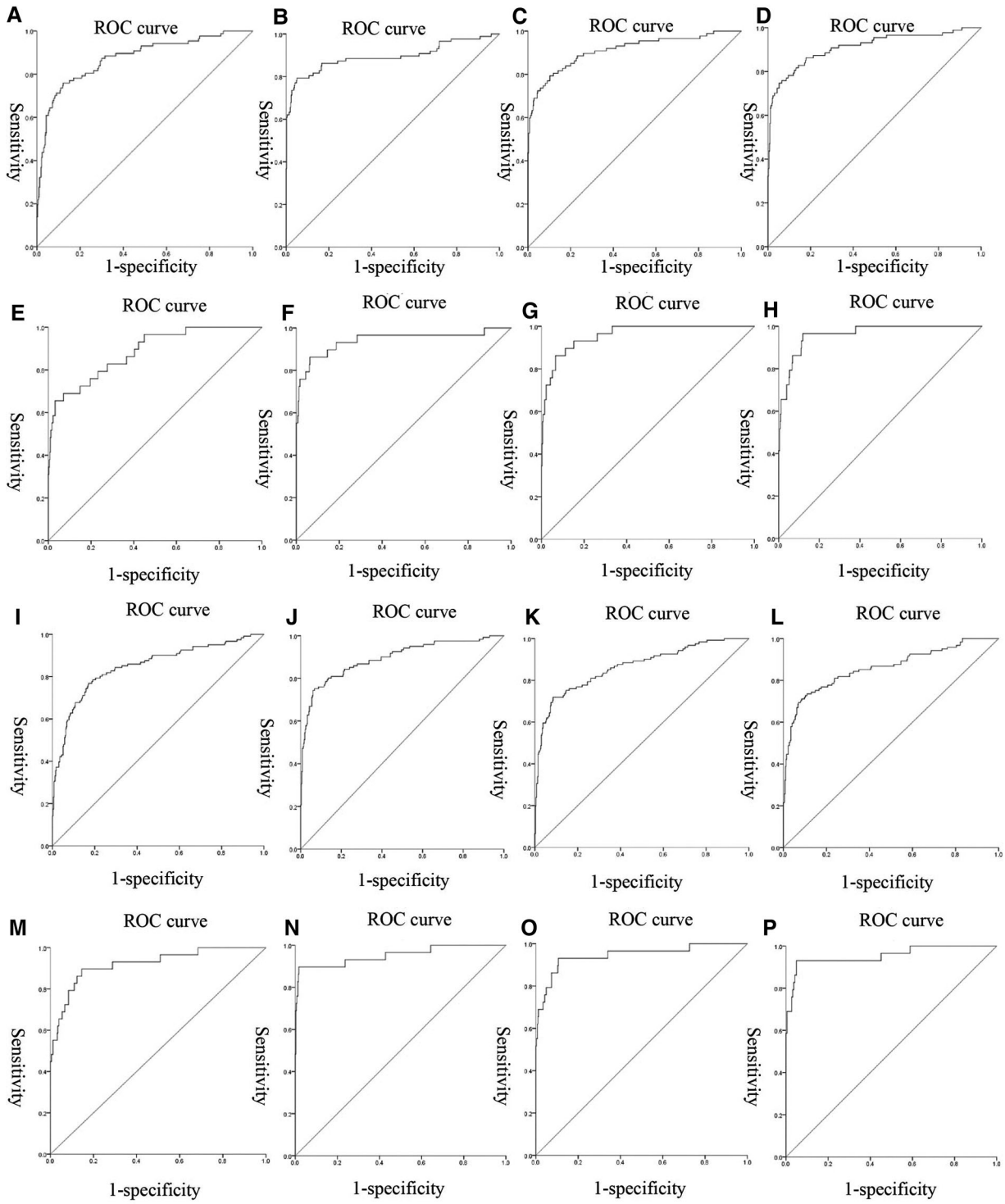

FIGURE 1
ROC curves of the models: (A–D) were the ROC curves of the four models of gestational hypertension; (E–H) were the ROC curves of the four models of early-onset preeclampsia; (I–L) were the ROC curves of the four models of early-onset preeclampsia; (M–P) were the ROC curves of the four models of chronic hypertension complicated with preeclampsia.

TABLE 12 Test results of the models.

Group	Model	*P*	AC (%)	SE (%)	SP (%)	AUC (95% CI)
GH	NLR	<0.001	79.25	79.31	79.24	0.873 (0.828–0.918)
	SVM	<0.001	93.08	72.41	97.37	0.894 (0.844–0.944)
	Step	<0.001	89.13	74.71	92.12	0.910 (0.870–0.951)
	Lasso	<0.001	90.32	75.86	93.32	0.910 (0.870–0.951)
EOPE	NLR	<0.001	77.40	75.86	77.51	0.884 (0.818–0.950)
	SVM	<0.001	95.66	75.86	97.07	0.940 (0.879–1.000)
	Step	<0.001	90.64	86.21	90.95	0.959 (0.929–0.989)
	Lasso	<0.001	91.78	86.21	92.18	0.962 (0.934–0.991)
LOPE	NLR	<0.001	80.38	76.86	81.45	0.847 (0.803–0.891)
	SVM	<0.001	88.27	62.81	95.99	0.894 (0.857–0.931)
	Step	<0.001	85.19	71.90	89.22	0.863 (0.822–0.905)
	Lasso	<0.001	85.58	72.73	89.47	0.859 (0.816–0.903)
CHCP	NLR	<0.001	83.91	89.66	83.50	0.921 (0.863–0.979)
	SVM	<0.001	97.70	75.86	99.26	0.952 (0.900–1.000)
	Step	<0.001	93.33	79.31	94.33	0.945 (0.893–0.998)
	Lasso	<0.001	91.72	93.10	91.63	0.955 (0.906–1.000)

NLR, nonlinear regression; SVM, support vector machine; Step, stepwise regression; Lasso, Lasso regression; AC, accuracy; SE, sensitivity; SP, sensitivity; AUC, area under the ROC curve.

TABLE 13 Parameters of the stepwise regression dynamic prediction model for the early-onset preeclampsia.

Factor	Coefficient
Gestational weeks	−1.12E−01*
Multiple pregnancy	3.25E+00**
History of spontaneous abortion	8.05E−01*
BMI	3.53E−01**
MAP	9.99E−02**
CO	−6.25E−01
CI	1.22E+00*
PlGF	−1.47E−02*
AST	−1.59E−01*
UA	1.66E−02**
Constant term	−1.79E+01**

BMI, body mass index; MAP, mean arterial pressure; CO, cardiac output; CI, cardiac index; PlGF, placental growth factor; AST, alanine aminotransferase; UA, uric acid.
*$P < 0.05$.
**$P < 0.01$.

regression dynamic prediction model for early-onset preeclampsia (Table 13), the predictive effect of PlGF in gestational hypertension, late-onset preeclampsia, and chronic hypertension complicated with preeclampsia was not significant, with parameter term coefficients of −3.26E−03, −1.39E−04, and −6.11E−03, respectively.

The validation results showed that Lasso regression prediction model had the highest accuracy among the four prediction models in the chronic hypertension complicated with preeclampsia (Table 14).

TABLE 14 Validation results of the prediction models.

Group	Model	AC (%)	SE (%)	SP (%)
GH	NLR	93.33	100.00	86.67
	SVM	83.33	66.67	100.00
	Step	86.67	73.33	100.00
	Lasso	86.67	73.33	100.00
EOPE	NLR	80.00	93.33	66.67
	SVM	73.33	46.67	100.00
	Step	96.67	93.33	100.00
	Lasso	83.33	66.67	100.00
LOPE	NLR	80.00	73.33	86.67
	SVM	66.67	100.00	33.33
	Step	73.33	53.33	93.33
	Lasso	76.67	53.33	100.00
CHCP	NLR	83.33	100.00	66.67
	SVM	66.67	33.33	100.00
	Step	100.00	100.00	100.00
	Lasso	100.00	100.00	100.00

NLR, nonlinear regression; SVM, support vector machine; Step, stepwise regression; Lasso, Lasso regression; AC, accuracy; SE, sensitivity; SP, sensitivity.

Discussion

Hypertensive pregnancy in disorders are pregnancy-specific systematic disorders that globally affect 5%–10% of all pregnancies (33, 34). We performed a comprehensive screening of high-risk factors for gestational hypertension, early-onset preeclampsia, late-onset preeclampsia and chronic hypertension combined with preeclampsia, which through the acquisition of clinical medical records of patients. For each HDP subtype, we constructed dynamic prediction models using nonlinear regression, support vector machines, stepwise regression, and Lasso regression. The results showed that the Lasso regression dynamic prediction model had the best prediction effect for the four HDP subtypes, which could help clinicians accurately assess the risk of HDP.

We compared the AUC of the four prediction models for each HDP subgroup, and we found that the AUC of the Lasso regression prediction model was higher than the other three prediction models. The accuracy of Lasso regression prediction model was over 85% for each HDP subgroup, and 91.78% for EOPE subgroup was the highest (Table 12). External validation of the model through the validation set, we found that Lasso regression prediction model had a good identification effect, with the accuracy of 86.67%, 83.33%, 76.67% and 100.00% for each HDP subtype, respectively (Table 14). Lasso regression allows automatic filtering of model parameters, and the Lasso regression model simplifies the input parameters of the model and makes the model structure simpler (Table 13).

PlGF is a member of the vascular endothelial growth factor family and has important functions in regulating placental trophoblast and endothelial cell function (35). Numerous studies have shown that PlGF is a risk factor for HDP and has a predictive value for preeclampsia in particular (36, 37).

PlGF was tested significant only in the stepwise regression model for the early-onset preeclampsia, which indicated a significant predictive effect of PlGF on the early-onset preeclampsia (Table 13).

Finally, there were some limitations in this research. First, this research was carried out in China, and the medical records used for model construction were all from pregnant Chinese women. Due to differences among regions and races, the applicability of the model to other countries needs to be further verified. Second, we developed prediction models for the four HDP subtypes in this study and found that the lasso regression prediction model had the best prediction effect, so it was impossible to explore the predictive ability of other HDP subtype.

Conclusion

We investigated the predictive effect of different variable selection and modeling approaches on HDP subtypes, and found the Lasso regression prediction model performed well and accurately predicted the risk of HDP subtypes. The Lasso regression prediction model provided corresponding guidance and served as a basis for preventing adverse outcomes and improving clinical treatment.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Science and Technology of Beijing University of Technology. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XZ, LY, and GL: conception and design of the research. QX, GL, and GS: acquisition of data. XZ, GS, and QX: analysis and interpretation of the data and statistical analysis. LY, DH, YY and XL: funding acquisition. XZ: writing of the manuscript. LY, CL, ZL, and XZ: critical revision of the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Perioperative management of acute myocardial infarction in the 31st week of pregnancy: A case report and literature review

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Pregnancy-related acute myocardial infarction (PAMI) is rare but life-threatening. The incidence of PAMI is growing over time for multiple reasons, and the management of parturients with acute myocardial infarction is challenging in terms of diagnosis and treatment. To date, there are still no clear guidelines on the best practice for PAMI. We present a case of a 41-year-old woman with PAMI at 31 weeks of pregnancy. Through multidisciplinary collaboration, successful outcomes were achieved for both the mother and fetus.

KEYWORDS

pregnancy-related acute myocardial infarction (PAMI), anesthesia management, case report, pregnancy, multidisciplinary collaboration

Introduction

Pregnancy-related acute myocardial infarction (PAMI) is relatively infrequent but is associated with notable maternal or fetal morbidity and mortality (1). The incidence of PAMI ranges from 0.06 to 10 per 100,000 pregnant women globally (2), with a case-fatality rate of 4.3% to 37% (3–5). The rate of PAMI is growing over time due to multiple reasons, such as rising maternal age and increased prevalence of obesity and diabetes (6). Spontaneous coronary artery dissection (SCAD) is a main etiology of PAMI and has been reported to occur in 15% to 40% of acute coronary syndrome (ACS) cases during pregnancy (2). To date, there are still many gaps in the understanding of PAMI, as guidelines for the management of PAMI are still limited (7). Management of puerperae suffering acute myocardial infarction could present significant clinical challenges to perinatal multidisciplinary teams (1, 8). We describe a case of a 41-year-old woman with PAMI at 31 weeks of pregnancy. Written informed consent was received prior to publication of this report.

Case report

A 41-year-old woman at 31 weeks gestation, gesta3, para1, with a history of previous correction surgery of patent ductus arteriosus, was admitted to the emergency department (ED) after suffering sudden crushing pain in the precordial area, accompanied by radiation on the left shoulder and back, toothache for 4 h.

Electrocardiogram (ECG) showed ST-segment elevation in leads I, aVL, and V2–V6 (Figure 1) and the myocardial enzymes increased. The echocardiography demonstrated segmental wall dyskinesia (apex, interventricular septum) and the left ventricular ejection fraction (LVEF) was estimated to be 59.5%. In view of the patient's symptoms, signs and test results, the patient was diagnosed with ST-segment elevation myocardial infarction (STEMI). Epidemiological investigation of the patient on admission revealed that she had no history of COVID-19 infection and was not vaccinated due to pregnancy. The patient had no previous history of angina pectoris and no risk factors, such as hypertension, diabetes, smoking, alcohol consumption or family history of coronary heart disease. Therefore, spontaneous coronary dissection was highly suspected.

The patient's symptoms were not relieved, so an interventional cardiologist performed emergent percutaneous coronary intervention (PCI) for the puerpera. Cardiac angiography showed that the left anterior descending (LAD) artery was 100% occluded (Figure 2), and the right coronary artery showed no obvious abnormalities. After the guiding wire passed through the occlusion, the blood flow of the anterior descending artery was opened (Figure 2). Stent placement was recommended for the patient due to unstable status, but the placement was unsuccessful owing to complex lesions.

A multidisciplinary team including an obstetrician, cardiologist, anesthesiologist, pediatrician and pharmacologist was established. The MDT considered pregnancy before 34 weeks has a high risk of cardiovascular events and low fetal survival and eventually reached a consensus that cesarean section would be performed two weeks after PAMI.

Cesarean section was scheduled at 34 weeks and 3 days of gestation. After the patient entered the operating room, electrocardiography, pulse oxygen saturation, invasive blood pressure and bispectral index (BIS® Sensor; Aspect Medical Systems, Natick, MA, USA) monitoring were routinely monitored. Endotracheal intubation was performed after induction. Anesthesia was maintained using sevoflurane and remifentanil. Intraoperative temperature monitoring was performed with a temperature probe. Forced air warming and warmed intravenous fluids were used to maintain the patient's core temperature. A transesophageal echocardiographic probe was then inserted, and cardiac function was monitored in real time. The examination showed decreased left ventricular function. There were multiple wall motion abnormalities, including apical septal dyskinesia (Figure 3). No valvular abnormalities were noted. At the same time, the FloTrac/Vigileo System (Edwards Lifesciences, Irvine, CA) was applied for hemodynamic monitoring. Five minutes after intubation, a 2,300 g female baby was born. The Apgar scores for the neonates were 8 and 10 at 1 min and 5 min, respectively. No respiratory depression was observed in the neonate, and she was transferred to the NICU. We administered 10 μg of sufentanil to the woman after the baby was delivered. The total volume of crystalloid fluids administered was 600 ml, and blood loss at the end of cesarean delivery was approximately 400 ml. Ultrasound-guided transversus abdominis plane block was performed after cesarean section. The patient was safely extubated and then admitted to the cardiac care unit (CCU) with a sufentanil patient-controlled analgesia pump.

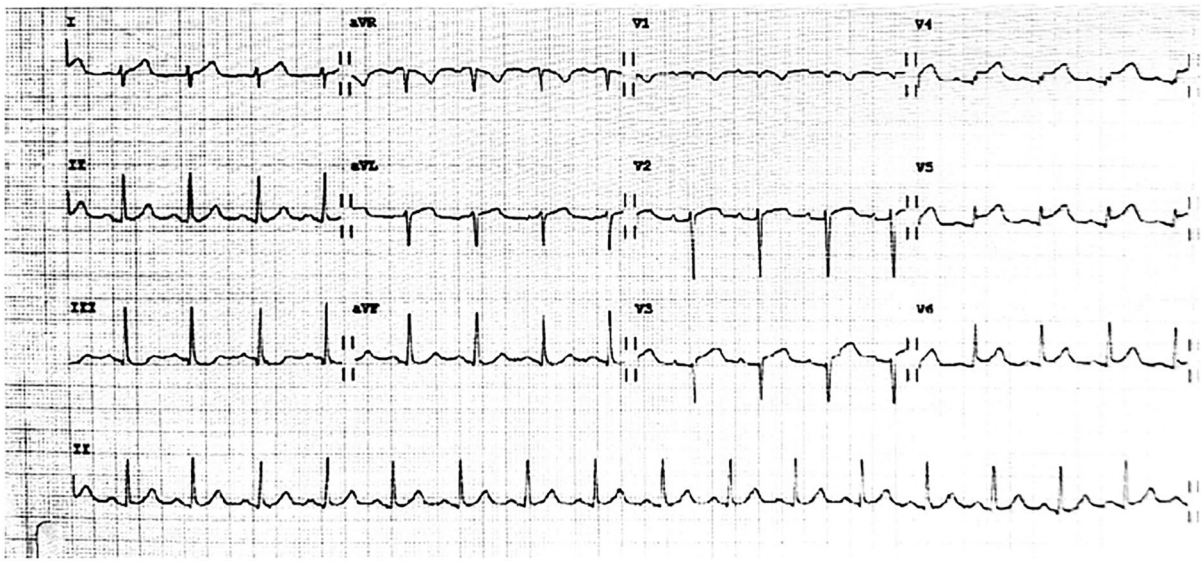

FIGURE 1
Twelve-lead electrocardiogram showed ST-segment elevation in leads I, aVL, and V2-V6.

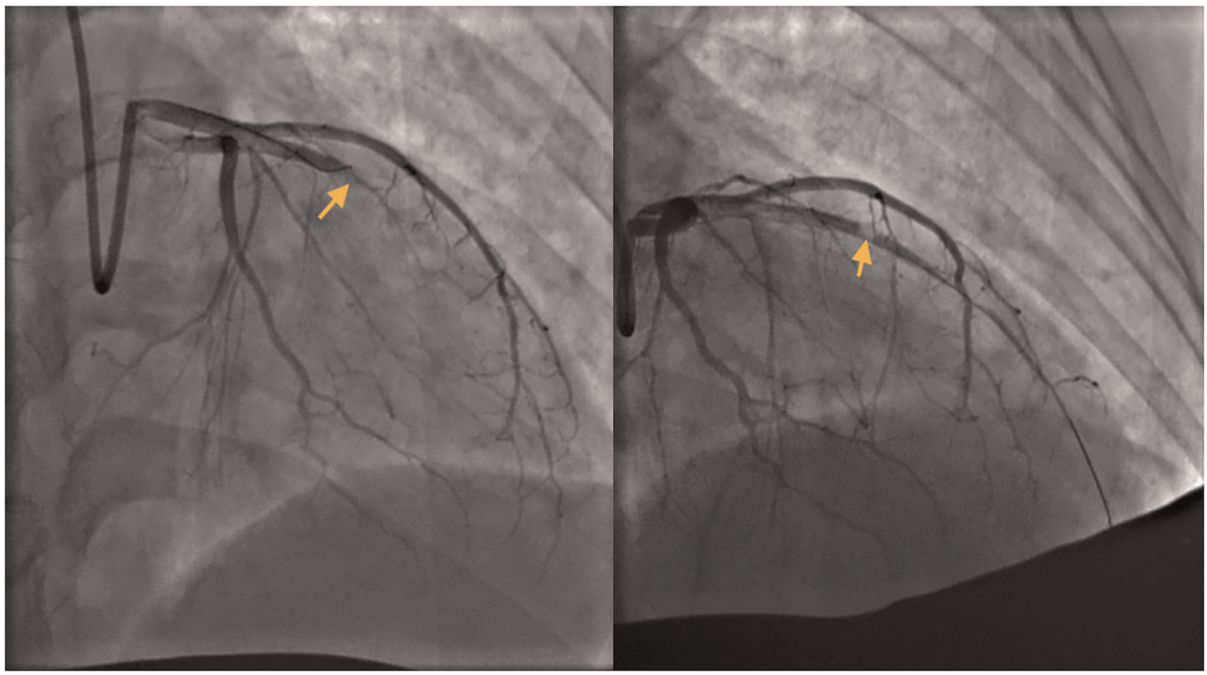

FIGURE 2
Left: Left anterior descending (LAD) artery: critical lesion in mid LAD. Right: The guide wire passed through the occlusion.

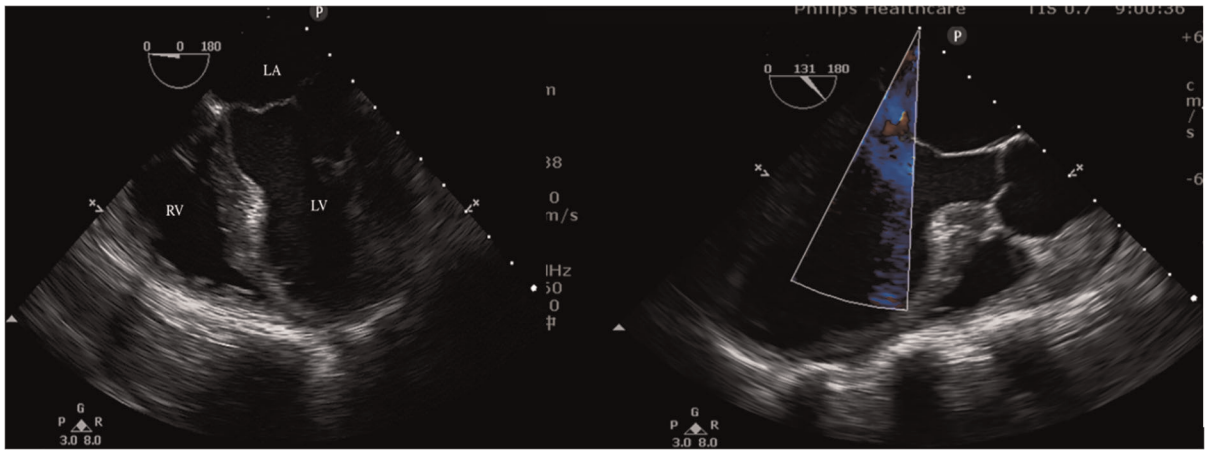

FIGURE 3
Intraoperative transesophageal echocardiograms.

She was monitored for 6 days postoperatively in the CCU, without postpartum hemorrhage, anginal symptoms or ECG changes. Echocardiographic examination did not show significant alterations, and myocardial enzymes showed no evidence of new ischemia.

Ten days after the cesarean section, the patient was discharged from the hospital. The patient and the child performed well at 6-month and one-year follow-up.

Discussion

PAMI is different from AMI in general patients in terms of etiology, diagnosis, and therapy. The management of pregnant patients with acute myocardial infarction is challenging and requires close cooperation between the obstetrician, cardiologist, neonatologists and anesthesiologist. Therefore, we need to better understand the pathophysiology and

management of PAMI and formulate an individualized anesthesia protocol for maternal and fetal safety.

The etiology and risk factors

Cardiovascular disease during pregnancy is the most common cause of pregnancy-associated mortality (9). AMI can occur throughout pregnancy but is more likely in the third trimester. PAMI is a multifactorial disease caused by multiple predisposing factors, such as hypertensive syndromes, known coronary artery disease (CAD), hyperlipidemia, thrombophilia states, substance abuse history, smoking history, obesity, multiple comorbidities, medicaid insurance status, and black race (6). Age >35 years is one of the most consistently reported risk factors for PAMI (10). The etiology of CAD in pregnancy differs from that in the general population; most CAD has nonatherosclerotic mechanisms, including pregnancy-related spontaneous coronary artery dissection (*P*-SCAD) (43%), angiographically normal coronary arteries (18%) and coronary thrombosis (17%) (6).

Multidisciplinary collaboration

Pregnant women with cardiac disease require appropriate anesthesia, cardiac, and obstetric management during the perinatal and postpartum period. Guidelines from the American Heart Association (AHA), European Society of Cardiology (ESC), Society of Maternal Fetal Medicine (SMFM) and American College of Obstetricians and Gynecologists (ACOG) suggest a "Pregnancy Heart Team" care for pregnant patients with complicated cardiac disease (11). In our case, a multidisciplinary team including an obstetrician, cardiologist, anesthesiologist, pediatrician and pharmacologist was established to assess the severity of cardiovascular disease, develop treatment and delivery planning.

Percutaneous coronary intervention

Myocardial revascularization and the rapid establishment of optimal cardiac treatment to limit cardiac remodeling are emergency interventions to improve maternal cardiac prognosis. The goal of management in the acute phase is to restore or preserve myocardial perfusion and cardiac function. The majority of AMI during pregnancy is caused by spontaneous coronary hematoma/dissection. The mechanism is unknown and may be related to changes in hormone levels during pregnancy. The mechanism of atherosclerosis is completely different from that of common AMI patients. In principle, if coronary angiography suggests a subintimal hematoma, as long as the vessel is not completely occluded and forward blood flow exists, then PCI is not recommended. Otherwise, the subintimal hematoma will extend and cause more problems. Generally, the hematoma is completely absorbed, and the blood vessel returns to normal in approximately one month. However, it was impossible to distinguish whether it was a hematoma or a thrombosis secondary to common plaque rupture during angiography in this patient; moreover, the blood vessel was completely occluded, so interventional treatment had to be performed. It was very difficult to pass the guiding wire, and guiding wires with different hardnesses were replaced three times. Finally, the occlusion segment was forcibly passed with the assistance of the microcatheter. Angiography showed no calcification in the local area. Any new devices, including balloons, stents, and intravascular ultrasound catheters, could no longer pass through the occlusion, and the cardiologist determined that it was caused by endothelium prolapse, which blocked the lumen. On the other hand, the biggest concern of PCI in pregnancy is radiation exposure. According to previous research, the radiation exposure of patients during procedures such as coronary angiography is estimated to be <20 mGy, while the fetal share of radiation is estimated to be 0.074 mGy. At doses below 50 mGy, there is a negligible risk of fetal teratogenicity following radiation exposure, while fetal damage may occur at doses above 150 mGy (2). Therefore, we believe that the radiation dose in coronary angiography is safe for most pregnant patients.

Antiplatelet therapy

Research on antiplatelet drugs is limited because pregnant and breastfeeding women are often excluded from these studies. Low-dose aspirin appears to be safe and can be continued during delivery (1, 9, 10). For patients whose main mechanism is spontaneous subintimal hematoma, it is generally not recommended to take antiplatelet and anticoagulant drugs (and statins) to avoid aggravating subintimal hemorrhage. However, in this case, the patient had undergone PCI because of endothelium prolapse and subsequent blocking of the lumen. The blood flow was restored by PCI with severe residual stenosis, and the stent was not successfully implanted. Therefore, antiplatelet drugs were administered to prevent the reocclusion of blood vessels caused by local thrombosis.

Anticoagulation therapy

Anticoagulation with heparin in pregnant patients is considered safe, as it does not cross the placenta and therefore has no teratogenic effect. Low molecular weight heparin (LMWH) is generally the preferred agent due to its easier

administration and more predictable effect. Neuraxial anesthesia should be avoided for at least 12 h after subcutaneous prophylactic dose of LMWH and at least 24 h for therapeutic dose of LMWH according to The American Society of Regional Anesthesia (ASRA) Guidelines and the SOAP Consensus Statement (12, 13).

Timing of delivery

For women with acute myocardial infarction during pregnancy, choosing the right timing for delivery is crucial. In the case of acute myocardial infarction, delivery should be postponed a few weeks after AMI to reduce hemodynamic stress immediately after the event (9), if possible, for at least two weeks from the time of infarction. In previous relevant case reports, most patients underwent elective cesarean section or vaginal birth after two weeks (**Table 1**). The risk of myocardial infarction complications was high within 2 weeks after AMI, and the fetal lung was immature. Considering the improved cardiac function after two weeks of medical treatment, a multidisciplinary team decided to postpone cesarean section until 34 gestational weeks.

Mode of delivery: Vaginal or cesarean delivery?

There is no general consensus on the recommended mode of delivery for pregnant women with AMI. The advantages of vaginal delivery include less blood loss and a lower risk of infection, venous thrombosis, and embolism and should be recommended for most women (9). Mihaljevic et al. (19) reported two cases of women with PAMI, one of whom was submitted to vaginal delivery due to her good clinical status. Cesarean section (CS) appears to be the most stable and controllable delivery method for parturients suffering from an acute cardiac event because it allows better control of labor time and prevents stress responses due to prolonged vaginal childbirth. The rate of CS in pregnancy-onset ischemic heart disease (IHD) is 62%–84.6% (20, 21). Elective CS generally does not improve maternal or fetal outcomes in women with stable heart disease. Baris et al. (20) considered that elective CS should be mainly recommended for high-risk obstetric indications, such as after a recent AMI or if the left ventricular ejection fraction continues to decline. However, the risk of having an adverse cardiovascular event was significantly greater in the cesarean group than in the vaginal delivery group (22), and the multidisciplinary team needs to pay more attention to maternal recovery after surgery. Roth et al. (23) in their review, held the opinion that the mode of delivery in patients with PAMI should be determined by obstetric indications and the clinical status of the mother. An appropriate and individualized decision based on the clinical status of the patient is the key for the optimal mode of delivery.

Anesthetic technique: Regional anesthesia or general anesthesia?

The decision to choose regional or general anesthesia is multifaceted. Both regional and general anesthesia have advantages and disadvantages in pregnant women with acute myocardial infarction. It is preferred to choose neuraxial anesthesia for cesarean delivery whenever possible in women with cardiac disease (11). In Yildırım's study (24), the proportion of regional and general anesthesia used during cesarean section was similar among parturients with heart disease, but it was observed that general anesthesia was mainly preferred for parturients with higher NYHA classifications, requiring emergency surgery, history of previous cardiac surgery or medication, and stage 3 or higher multiple valvular disease. Gil et al. (15) reported a case of PAMI presenting for CS under general anesthesia. They used rapid sequence induction with rocuronium and etomidate. The patient was monitored with direct blood pressure and central venous pressure and did not present clinical signs of hemodynamic instability during the

TABLE 1 Summary of case reports of anesthesia management for acute myocardial infarction (AMI) in pregnancy.

Ref.	Type	Maternal age	PAMI time	LVEF	Timing of delivery	Mode of Delivery	Anesthesia tenique
Hands et al (14), 1990	Case report	26	38 weeks	UK	40 weeks	CS	Epidural anesthesia
		31	36 weeks	48%	64 h after AMI	CS	Epidural anesthesia
Gil et al (15), 2006	Case report	31	38 weeks	57%	38 weeks	CS	General anesthesia
Duarte et al (16), 2011	Case report	39	31 weeks	30%	35 weeks	CS	Epidural anesthesia
Pougeoise et al (17), 2012	Case report	32	38 weeks	45%	25 h after AMI	CS	General anesthesia
Frassanito et al (18), 2012	Case report	36	25 weeks	57%	35 weeks	CS	General anesthesia
Mihaljevic et al (19), 2015	Case report	32	20 weeks	41%	38 weeks	CS	General anesthesia
		35	30 weeks	68%	38 weeks	Vaginal birth	Epidural anesthesia

PAMI, pregnancy-related acute myocardial infarction, AMI, acute myocardial infarction, LVEF, left ventricular ejection fraction, UK unknown, CS, cesarean section.

course of the surgery. Considering that the woman was in the acute phase of myocardial infarction and was being treated with oral anticoagulants, the MDT decided to perform a cesarean section under general anesthesia.

Intraoperative anesthesia monitoring techniques

Intraoperative anesthesia management goals include ensuring coronary perfusion and avoiding tachycardia and excessive ventricular end-diastolic volume, maintaining cardiac output and myocardial contractility, adequate arterial oxygen content, and maintaining body temperature and internal environment stability.

Adequate hemodynamic monitoring is essential to reduce perioperative morbidity and mortality in cardiac patients. On the one hand, intraoperative transesophageal echocardiography (TEE) can be used as an important tool to dynamically monitor the changes in cardiac function of patients with severe comorbidities or if hemodynamic instability is expected or occurs intraoperatively. In the absence of ECG changes during myocardial ischemia, regional wall motion abnormalities have been reported in a significant proportion of patients. Because mechanical abnormalities (systole and diastole) precede electrical abnormalities during ischemia, TEE has the advantage of early identification of myocardial ischemia (25). On the other hand, the FloTrac/Vigileo system provides important information on hemodynamic status, such as cardiac output (CO), cardiac index (CI), stroke volume (SV), and stroke volume variation (SVV) (26) and it provides a useful method to determine the differential diagnosis of circulatory failure, especially to distinguish among cardiac factors, vascular factors, and blood volume. Consequently, it provides a method to monitor hemodynamic status, changes in the clinical course and responses to therapeutic interventions in patients who have arterial catheters in place. This technique may be potentially useful and suitable for high-risk pregnant women to guide therapy with fluids and vasoactive drugs. As far as we know, this is the first case to describe the application of FloTrac/Vigileo and TEE for cesarean delivery.

Postoperative analgesia

The postpartum period is a time of increased risk of cardiovascular disease-related maternal morbidity and mortality (27). Postoperative pain is an important risk factor that contributes to postoperative myocardial ischemia and MI (28). Cesarean section can cause moderate to severe acute postoperative pain. Improper postoperative pain control may delay the mother's recovery, interfere with breastfeeding, and have a negative influence on mother-infant bonding (29). Therefore, it is important for anesthesiologists to seek optimal postoperative analgesia for parturients with cardiac disease. At present, multimodal analgesic strategies, including neuraxial anesthesia, peripheral nerve blocks, and administration of nonopioid analgesics, are widely performed after cesarean section. In the past, it was reported in the literature (16, 26) that neuraxial anesthesia for women with acute myocardial infarction who underwent cesarean section after stopping antiplatelet drugs before surgery has been shown to provide safe and superior postoperative analgesia and keep hemodynamic parameters more stable. For parturients undergoing general anesthesia, postoperative patient-controlled intravenous analgesia with sufentanil (PCA) plus TAP block is an alternative to neuraxial analgesia. USG-TAP block provides effective analgesia in women receiving CS, helps improve the severity of nausea and vomiting, and has good maternal satisfaction (30). During the postoperative follow-up, the patient was satisfied with the analgesic effect.

Conclusion

The management of parturients with acute myocardial infarction is challenging in terms of diagnosis and treatment, and successful outcomes for both the mother and fetus come from the efforts of a multidisciplinary team of obstetricians, cardiologists, anesthetists and pediatricians. There are still no clear guidelines on the best practice for the PAMI. Our case demonstrates that multidisciplinary collaborative management, precise timing of surgery, and individualized perioperative management may help improve maternal outcomes and neonatal health for pregnant women with PAMI undergoing cesarean delivery.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

PS was responsible for drafting of the manuscript and collecting the relevant data. XQL was responsible for collecting the relevant data. TH was responsible for revision of the manuscript. HZ was responsible for the conception of the review, supervision, and

critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Impact of offspring endothelial function from *de novo* hypertensive disorders during pregnancy: An evidence-based review

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De novo hypertensive disorders of pregnancy (HDP) which consist of gestational hypertension and preeclampsia affect maternal and offspring morbidity and mortality, and potentially increase the risk of cardiovascular disease in the offspring. It is well known that *de novo* HDP causes various maternal complications, including cardiovascular diseases, placental abruption and liver and kidney failure. However, there are studies suggesting that offspring of pregnancies complicated by *de novo* HDP have an increased risk of long-term cardiovascular disease. The endothelium is an important regulator of vascular function, and its dysfunction is highly associated with the development of cardiovascular diseases. Hence, this review aimed to systematically identify articles related to the effect of *de novo* HDP on the endothelial function of the offspring. A computerized database search was conducted on PubMed, Scopus, and Medline from 1976 until 2022. A total of 685 articles were obtained. We identified another three additional articles through review articles and Google Scholar. Altogether, we used 13 articles for data extraction. All studies reported that endothelial function was impaired in the offspring of *de novo* HDP. This is most likely attributed to impaired vasodilation, subclinical atherosclerosis formation, inflammation, and dysregulated epigenetic regulation of endothelial functions.

KEYWORDS
hypertensive disorders of pregnancy, preeclampsia, endothelial function, offspring, cardiovascular disease

Introduction

Hypertensive disorders of pregnancy (HDP) are the most common medical disorder during pregnancy. HDP shows an increasing incidence rate globally with a total increase of 10.92% from 1990 to 2019 (1). The International Society for the Study of Hypertension in Pregnancy (ISSHP) classified HDP as chronic (pre-dating pregnancy or diagnosed

prior to 20 weeks of pregnancy) or *de novo* (gestational hypertension or preeclampsia) (2, 3). Among all, preeclampsia (PE) was the most complex disorder, deteriorating rapidly with more than 70,000 maternal deaths and 500,000 fetal and neonatal deaths per year (2).

A previous study revealed that women with HDP have a higher tendency to have neonatal adverse outcomes than normotensive women (4). Alongside the complications of HDP to the mother, HDP also has short- and long-term adverse effects on the offspring. In the short term, neonates of mothers with HDP have a high risk of developing fetal hypoxia, premature birth, placental abruption, low birth weight, small for gestational age, respiratory distress syndrome, and death *in utero*. In the long term, neonates develop hypertension, arterial thickening, increased left ventricular wall thickness and reduced left ventricular end-diastolic volume (5).

Studies also found that HDP increases the risk of hypertension and cardiovascular disease (CVD) not only to the mother, but also to the offspring (6–8). The relevance of HDP on the offspring's health extends into adulthood. The HUNT study showed that as young adults, the offspring of women with HDP have higher CVD risk in terms of higher blood pressure (BP), body mass index (BMI) and waist circumference compared to the offspring of women with normal pregnancies (6).

HDP is considered a maternal and fetal endothelial disorder. The endothelium is a functional organ formed by a single layer of squamous endothelial cells that line all blood vessels. Endothelial cells play a role in vascular homeostasis and angiogenesis in response to injury or hypoxia. Studies have demonstrated that in preeclampsia, endothelial dysfunction occurs in the vascular endothelium of both mothers (9) and offspring (10). Preeclampsia is also the most common HDP that is associated with endothelial dysfunction (11).

Preeclampsia starts when placental perfusion is reduced by abnormal cytotrophoblast invasion of the spiral arteries (12). The imbalance between pro- and anti-angiogenic factors in preeclampsia is proposed to trigger the abnormal placental vascularization and the onset of preeclampsia (13). The dysfunctional placentation causes oxidative stress and increased resistance to placental blood flow. Subsequently, hypoperfusion, chronic placental ischemia (5) and endothelial dysfunction ensue (14). Endothelial dysfunction alters the capacity of endothelial cells to maintain homeostasis and leads to the development of CVD (15). Additionally, the premature offspring of women with preeclampsia had changes in their endothelial function from early life and a high risk to develop hypertension later (10).

The impact of *de novo* HDP on the offspring's endothelial function has just started to be valued. Most reviews highlight the effect of *de novo* HDP on maternal endothelial function, while the review on *de novo* HDP's effect on the offspring is limited, particularly the ones involving clinical studies. Therefore, this systematic review is aimed to evaluate the current database related to the outcome of *de novo* HDP, which includes gestational hypertension and preeclampsia, on endothelial function of human offspring *in utero*, at birth and long term.

Method

Search strategy

We identified the relevant studies on the effect of *de novo* HDP on offspring endothelial function using three electronic databases; PubMed, Scopus and Medline which were assessed between 1976 and 2022. The search strategy involved a combination ("AND") of the following three sets of keywords: (1) Hypertension in pregnancy OR pre-eclampsia OR maternal hypertension OR gestational hypertension; (2) endothelial OR endothelial function OR endothelial dysfunction OR endothelial cell; and (3) neonate OR neonatal OR offspring OR fetal OR children. During the search, an asterisk (*) was used in Scopus as a truncation sign to broaden the search to include various word endings. We also searched the list of references of the articles selected for relevant citations.

Inclusion and exclusion criteria

Studies that fulfill the following criteria were included: (i) studies that investigated the effects or association of *de novo* HDP (gestational hypertension or preeclampsia) on offspring endothelial function, (ii) human studies, (iii) studies published from 1976 to 2022, and (iv) articles published in English. The following studies were excluded: (i) studies that investigated the effects or association of chronic HDP on offspring endothelial function (ii) studies that associate CVD in neonates with congenital or other pathological changes unrelated to HDP (iii) review articles, meta-analyses, letters, newsletters, editorial, conference abstracts or case studies (iv) duplicated studies (v) animal studies and (iv) articles published in language other than English.

Screening of articles for eligibility and data extraction

Firstly, articles that did not match the inclusion criteria based solely on their titles were excluded. Then, the abstracts of the remaining articles were screened to exclude articles that did not match the inclusion criteria. Finally, the full text of the remaining articles was read and assessed completely. At least two reviewers assessed the articles. Discussion between reviewers was done to resolve any issues. The data were extracted using a data collection form. The following data

were extracted from the selected studies: (1) study population, (2) gestational/offspring age, (3) parameters measured, (4) findings, and (5) conclusion.

Results

Studies selected

The initial literature search conducted in PubMed, Scopus and MEDLINE *via* EBSCOhost databases identified 685 potentially relevant articles. In the first phase, 643 articles were excluded as the articles were not related to the effect of *de novo* HDP on the offspring endothelial function based on the titles, abstracts, and keywords. Furthermore, 30 articles were excluded for several reasons: articles that are not original research, animal studies, articles not written in English, and duplicate articles. A hand-selected or snowball search was performed using Google Scholar, and we added another three relevant articles. After assessment by the reviewers, 13 articles were included in this review. The steps involved in the article selection process are shown in **Figure 1**. Based on the 13 included studies, the effects of *de novo* HDP on offspring endothelial function were classified into three major effects, namely, the impact on vasodilation and subclinical atherosclerosis (**Table 1**), inflammation (**Table 2**), and epigenetic regulation of endothelial functions (**Table 3**).

Study characteristics

The study design, including the age of the offspring and the study population differed in several ways. The age of the offspring involved in the studies varied greatly. There were a few different life stages, namely prenatal age (19th-37th week of gestation) (16), neonates (aged less than four weeks old) (17–26), infants (aged 2–12 months old) (21), toddlers (aged 1–3 years old) (27), children (aged 5–12 years old) (27, 28) and adolescent (aged 12–19 years old) (27). The study population also varied. Nine of the studies involved the offspring of mothers with preeclampsia (18–20, 22–26, 28), while the remaining four studies involved the offspring of mothers with gestational hypertension (16, 17, 21, 27).

Impact of *de novo* HDP on offspring vasodilatation and subclinical atherosclerosis

A study by Touwslager et al. measured vasodilatation and perfusion of the offspring's skin microvasculature in response to acetylcholine (endothelium-dependent vasodilator) and nitroprusside (endothelium-independent vasodilator) using laser-Doppler device and iontophoresis. The maximum perfusion in the offspring's vasculature following acetylcholine administration, but not nitroprusside, was inversely associated with maternal HDP (17). In a 20-year follow-up study, offspring born preterm to either hypertensive or normotensive pregnancy had higher peripheral and central blood pressure than full-term born offspring (27). However, there were differences in their underlying vascular phenotype. Flow-mediated dilatation (FMD), which is the gold standard measurement for endothelial function, was lower in the preterm offspring of hypertensive pregnancies. The offspring also displayed a greater carotid intima-media thickness (IMT), a marker of subclinical atherosclerosis (27). In contrast, the preterm offspring of normotensive pregnancies had greater arterial stiffness than the offspring of hypertensive pregnancies (27). In another study, the fetus of mothers diagnosed with late gestational hypertension showed higher aortic IMT, umbilical artery pulsatility index (PI), fetal aorta PI and mean uterine arteries PI, which suggested subclinical atherosclerosis (16). In summary, the offspring from *de novo* HDP showed impaired vasodilatation and signs of subclinical atherosclerosis.

Impact of *de novo* HDP on offspring endothelial inflammation and function

Children of women with a history of severe preeclampsia and small for gestational age pregnancies had impaired endothelial function as evidenced by reduced reactive hyperemia index (RHI) measured five to eight years after birth. However, there was no significant change in their circulating inflammatory biomarker level (high-sensitivity C-reactive protein; hsCRP), and there was no significant correlation between their RHI and hsCRP level (28). Meanwhile, human umbilical vein endothelial cells (HUVEC) isolated from the offspring of mothers with preeclampsia showed lower nitric oxide (NO) levels. NO is an important vasodilator and a marker of endothelial function. This reduction in fetal endothelial NO level was associated with higher levels of maternal inflammatory markers (serum soluble endothelial leukocyte adhesion molecule-1 (sE-selectin) and vascular cell adhesion molecule 1 (VCAM-1)) (18). Furthermore, offspring coronary artery size is a useful parameter to assess the severity of neonate's endothelial inflammation and dysfunction due to maternal preeclampsia. It was demonstrated that the neonates of mothers with preeclampsia had higher VCAM-1 expression in their umbilical arteries and larger coronary arteries, suggesting that coronary artery size is an indicator of neonatal endothelial inflammation (19). Taken together, the studies suggested that *de novo* HDP promotes inflammation which contributes to offspring's endothelial dysfunction.

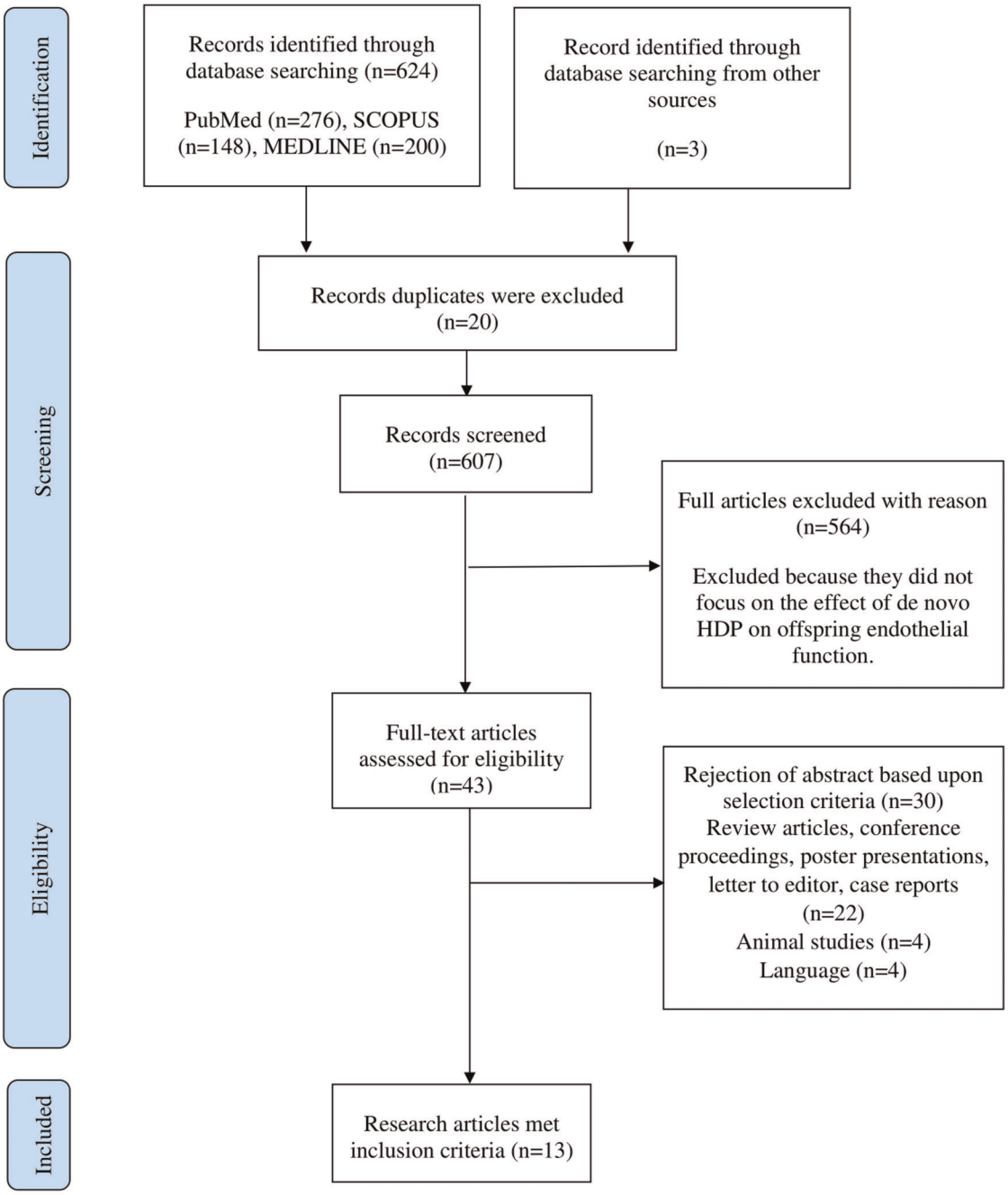

FIGURE 1
Summary of the steps involved in article selection process according to PRISMA guideline.

Impact of *de novo* HDP on offspring epigenetic regulation of endothelial function

Investigations on the epigenetic modifications of preeclampsia on offspring endothelial cells and endothelial progenitor cells (EPC) revealed an array of differentially expressed microRNAs (miRNAs or miRs), including hsa-miR-1270 (26), miR-29a/c-3p (20) and miR-146a (21). EPC are circulating cells that play an essential role in maintaining vascular function. Cord blood-derived fetal EPC from preeclampsia pregnancies had a different miRNA profile compared to healthy pregnancies. RNA sequencing analysis showed significant downregulation of hsa-miR-1270 in the EPC (26). The level of hsa-miR-1270 was

TABLE 1 Summary of the impact of *de novo* HDP on offspring vasodilation and subclinical atherosclerosis.

Refs	Study population	Gestational / Offspring age	Parameter (s)	Findings	Conclusion
(27)	- Preterm offspring of hypertensive pregnancies ($n = 71$) - Preterm offspring of normotensive pregnancies ($n = 52$) - Term offspring of normotensive pregnancies ($n = 38$)	18 months, 7 years, and 15 years old	- Peripheral and central SBP, DBP, MAP and PPBP - PWV, FMD, NMD and CIMT	- Offspring born preterm to either hypertensive or normotensive pregnancies displayed higher peripheral and central blood pressure compared to full-term born offspring. - Preterm offspring of normotensive pregnancies had greater arterial stiffness than offspring of hypertensive pregnancies. - Offspring of hypertensive pregnancies had higher CIMT and lower FMD.	Prematurity is associated with higher blood pressure in later life. Preterm offspring of hypertensive pregnancies have impaired endothelial function and greater subclinical atherosclerosis.
(17)	Healthy term newborns ($N = 104$)	First week of life	- Vasodilatation of the skin microvasculature in response to acetylcholine (endothelium-dependent vasodilator) and nitroprusside (endothelium-independent vasodilator)	- The maximum perfusion after administration of acetylcholine but not nitroprusside in the offspring was inversely associated with maternal hypertension.	Hypertension during pregnancy is inversely associated with endothelium-dependent vasodilatation of the offspring.
(16)	- Late onset gestational hypertension ($n = 50$) - Normotensive pregnancies ($n = 50$)	From 19th to 37th week of gestation	- Fetal aIMT, umbilical artery PI, fetal aorta PI and mean uterine arteries PI	- Fetuses of women affected by late gestational hypertension had higher fetal aIMT, umbilical artery PI, fetal aorta PI, and mean uterine arteries PI.	Gestational hypertension may predispose to impaired fetal cardiovascular development during intrauterine life.

Abbreviations: aIMT, Aortic intima-media thickness; CIMT, Carotid intima-media thickness; DBP, Diastolic blood pressure; FMD, Flow-mediated dilation; MAP, Mean arterial pressure; NMD, Nitrate-mediated dilatation; PI, Pulsatility index; PPBP, Pulse pressure blood pressure; PWV, Pulse wave velocity; SBP, Systolic blood pressure.

negatively correlated with the mRNA expression of its target gene, angiopoietin-related protein 7 (ANGPTL7) and transferrin receptor (TFRC). ANGPTL7 and TFRC are important proteins involved in angiogenesis and cellular iron uptake, respectively. Furthermore, inhibition of hsa-miR-1270 decreased tube formation capacity and chemotactic motility of the EPC (26). Taken together, the results suggested that preeclampsia caused overexpression of hsa-miR-1270, which led to impaired angiogenic function of the offspring EPC. This corresponds with another study that showed preeclampsia reduced the number and function of fetal EPC, which could be due to an increase in the anti-angiogenic factor; soluble fms-like tyrosine kinase 1 (sFlt-1) (23).

Meanwhile, downregulation of miR-29a/c-3p was observed in HUVEC isolated from the offspring of preeclampsia pregnancies. MiR-29a/c-3p inhibition impaired vascular endothelial growth factor A (VEGFA) and fibroblast growth factor 2 (FGF-2)-induced endothelial cell migration (20). Additionally, upregulation of miR-146a was observed in HUVEC isolated from the offspring of hypertensive pregnancies. Overexpression of miR-146a led to impaired endothelial tubulogenesis. A higher miR-146a expression was also associated with reduced microvascular density in the offspring at three months of life, which might increase the risk of developing hypertension later (21). In short, the findings indicate that preeclampsia altered the expression of an array of miRNAs, which caused significant dysregulation of the offspring endothelial function.

Endothelial colony forming cells (ECFC), which is a proliferative subtype of EPC, was found to be reduced in the cord blood of offspring from preeclampsia pregnancies (24). Genomic methylation pattern of fetal ECFC from preeclampsia pregnancies also differed from normal pregnancies, with 954 genes in passage three and 1,719 genes in passage five showing differentially methylated CpG sites (25). This difference in genomic methylation pattern of ECFC in preeclampsia might negatively impact the capacity of offspring endothelial development and repair functions (25). In another study, endothelial transcriptome profiling revealed dysregulation of 926 and 172 genes in HUVEC isolated from the male and female neonate of preeclampsia pregnancies, respectively. Many of the dysregulated gene networks are associated with CVD and endothelial function, such as tumor necrosis factor α (TNF-α), transforming growth factor beta-1

TABLE 2 Summary of the impact of *de novo* HDP on offspring endothelial inflammation and function.

(28)	- Offspring from PE pregnancies ($n = 26$) - Offspring from normal pregnancies ($n = 17$)	Five to eight years old	- Serum inflammatory biomarker (hsCRP) - RHI	- Lower RHI in children of PE with SGA pregnancies several years after birth. - No significant changes in the children's hsCRP levels. - No significant correlation between their RHI and hsCRP levels.	Children from PE pregnancies have reduced endothelial function.
(18)	- HUVEC isolated from the offspring of women with mild PE ($n = 7$) - HUVEC isolated from the offspring of women with severe PE ($n = 10$) - HUVEC isolated from the offspring of normotensive women ($n = 7$)	At birth	- NO level in HUVEC	- HUVEC isolated from the umbilical cords of offspring from PE pregnancies displayed lower NO level. - Lower fetal endothelial NO level was associated with higher levels of maternal inflammatory markers (serum sE-selectin and VCAM-1).	Decreased NO level in fetal endothelium born from PE pregnancies was associated with high levels of maternal inflammatory markers.
(19)	- Neonates of PE mothers ($n = 65$) - Neonates of normotensive mothers ($n = 404$)	At birth	- VCAM-1 in umbilical arteries - neonate coronary artery size	- Neonates of PE mothers had higher VCAM-1 expression in their umbilical arteries and larger coronary arteries at birth compared to neonates of normotensive women.	Coronary artery size is a useful severity index of neonatal endothelial inflammation due to PE.

Abbreviations: hsCRP, High-sensitivity C-reactive protein; HUVEC, Human umbilical vein endothelial cells; NO, Nitric oxide; PE, Preeclampsia; RHI, Reactive hyperemia; sE-selectin, Soluble endothelial leukocyte adhesion molecule-1; SGA, Small gestational age; VCAM-1, Vascular cell adhesion molecule 1.

(TGFβ1), FGF-2 and VEGFA (22). Further functional analysis showed a weakening of the endothelial monolayer integrity in HUVEC from female offspring in response to TNF-α. In the meantime, exposure to FGF-2 strengthened cell monolayer integrity in both male and female offspring endothelial cells. Preeclampsia also promoted TNF-α-, TGFβ1-, and VEGFA-induced proliferation of HUVEC from female offspring, but not in HUVEC from male offspring. In addition, preeclampsia inhibited TNF-α-induced migration of HUVEC of female offspring, with an opposite effect on HUVEC of male offspring (22). In summary, preeclampsia dysregulates the fetal endothelial transcriptome and endothelial function in a sex-specific manner, with female offspring more severely affected by preeclampsia than male offspring.

Discussion

De novo HDP disrupted offspring endothelial function by causing impaired vasodilatation, subclinical atherosclerosis formation, inflammation, and epigenetic dysregulation of endothelial functions (**Figure 2**).

HDP impairs vasodilatation and promotes subclinical atherosclerosis in the offspring

The endothelium is a thin membrane that lines the vascular network and plays an important role in vascular homeostasis. Maintaining the endothelium's structural and functional integrity is essential, particularly in balancing vasodilatation and vasoconstriction. Evidence suggests that offspring born to *de novo* HDP had impaired endothelium-dependent vasodilatation as measured by FMD (27), This result was in accordance with other studies done specifically in preeclampsia pregnancies (29, 30), indicating the possible increase in total peripheral resistance and blood pressure in the offspring. FMD is the gold standard method to measure endothelial function clinically. It is an ultrasound-based, non-invasive technique that measures endothelium-dependent vasodilatation in response to shear stress (31). However, further mechanistic studies are needed to fully understand the underlying mechanisms that contribute to the impaired vasodilatation in the offspring.

Microvascular structural changes can be seen in the offspring of mothers with HDP after birth due to heritable predisposition from the mothers or a reflection of intrauterine endothelial dysfunction (32). The aortic and carotid IMT are the markers of subclinical atherosclerosis, whereby IMT refers to the distance between the leading edge of the intimal interface and the leading edge of the media-adventitia interface at the outer part of the vessel (33). IMT is a well-established independent predictor of future CVD risk and previous studies have demonstrated a higher carotid IMT in children and adults with cardiovascular risk factors such as hypercholesterolemia (34), smoking (35) and family history of CVD (36). Fetuses of mothers with late gestational hypertension have higher aortic IMT detected at 29th -32nd

TABLE 3 Summary of the impact of *de novo* HDP on offspring epigenetic regulation of endothelial function.

Ref	Study population	Gestational / Offspring age	Parameter (s)	Findings	Conclusion
(20)	HUVEC isolated from the offspring of PE-complicated pregnancies ($n = 3$) and normotensive pregnancies ($n = 3$)	At birth between 36th – 39th week of gestation	- Differentially expressed miRNAs	- Sixteen differentially expressed-miRNAs including miR-29a/c-3p were downregulated in HUVEC isolated from PE pregnancies. - Knockdown of miR-29a/c-3p inhibited the FGF2-induced relative AKT1 phosphorylation in HUVEC - Knockdown of miR-29a/c-3p inhibited the VEGFA- and FGF2-induced endothelial cell migration in HUVEC.	PE dysregulates an array of miRNAs that may play important roles in fetal endothelial function. Downregulation of miR-29a/c-3p impairs the VEGFA- and FGF2-stimulated fetal endothelial cell migration.
(22)	HUVEC isolated from the offspring of PE-complicated pregnancies ($n = 5$-10) and normotensive pregnancies ($n = 5$-10)	At birth	- Endothelial transcriptome profile - Endothelial monolayer integrity, proliferation, and migration	- A total of 926 and 172 genes were dysregulated in HUVEC isolated from female and male offspring of PE pregnancies, respectively. - Many of the PE-dysregulated genes are associated with CVD and endothelial function. - TNF-α-, TGFβ1-, FGF2-, and VEGFA-regulated gene networks were differentially disrupted in female and male HUVEC from PE pregnancies. - PE decreased endothelial monolayer integrity in response to TNFα in both female and male HUVEC. - PE decreased TGFβ1-strengthened monolayer integrity in female HUVEC, while it enhanced FGF2-strengthened monolayer integrity in male HUVEC. - PE promoted TNF-α-, TGFβ1-, and VEGFA-induced cell proliferation in female, but not in male HUVEC. - PE inhibited TNF-α-induced cell migration in female HUVEC but had an opposite effect on male HUVEC.	Preeclampsia dysregulates the fetal endothelial transcriptome and endothelial function in a sex-specific manner, with female offspring are more affected by PE than male offspring.
(21)	- Offspring and HUVEC isolated from the offspring of hypertensive pregnancies ($n = 25$) and normotensive pregnancies ($n = 32$)	- At birth between 37th – 39th week of gestation and 3 months postnatal	- Differentially expressed miRNAs - Dermal microvascular density	- Endothelial cells from neonates of hypertensive pregnancies had different miRNA profile associated with altered endothelial phenotype. - The most upregulated miRNA was miR-146a. - miR-146a overexpression led to impaired *in vitro* endothelial cell tubulogenesis. - Higher miR-146a level in the HUVEC of an offspring was associated with reduced microvascular density in the neonate at three months of life.	Offspring of hypertensive pregnancies have altered endothelial regulatory microRNA profile at birth, which is related to impaired endothelial cell behavior that predicts the patterns of microvascular development during the first three months of life.

(*continued*)

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TABLE 3 Continued

Ref	Study population	Gestational / Offspring age	Parameter (s)	Findings	Conclusion
(25)	Cord blood derived fetal ECFC from late onset PE ($n = 12$) and normotensive pregnancies ($n = 12$)	At birth	- Genomic methylation pattern	- Fetal ECFC from PE pregnancies showed a differential methylation pattern compared to uncomplicated pregnancies, with 954 genes in passage three and 1,719 genes in passage five showing differentially methylated CpG sites. - ECFC from PE pregnancies are differentially methylated in regions corresponding to a broad range of processes regulating cell metabolism, transcription, and cell cycle. - Regarding PE, the pathways involved might negatively impact the capacity for endothelial development/repair and trophoblast invasion.	- Fetal ECFC methylation status differs between PE and normotensive pregnancies. An epigenetically modified endothelial precursor may influence both normal morphogenesis and postnatal vascular repair capacity.
(26)	Cord blood-derived fetal EPC from PE ($n = 12$) and normotensive pregnancies ($n = 9$)	- At birth	- miRNA profile - Tube formation, chemotactic motility, and cell proliferation	- Cord blood-derived fetal EPC from PE pregnancies had different miRNA profile compared to healthy pregnancies. - The most statistically different miRNA was hsa-miR-1270 in cord blood fetal EPC from PE pregnancies, and the level was negatively correlated with the mRNA expression of its target gene, ANGPTL7 and TFRC. - Hsa-miR-1270 inhibition significantly reduced the tube formation and chemotactic motility but had no effect on the cell proliferation.	Cord blood-derived fetal EPC from pregnancies complicated with PE have different miRNA profile compared to healthy pregnancies, with hsa-miR-1,270 being one of the most differentially expressed miRNAs.
(23)	Cord blood-derived fetal EPC from PE ($n = 14$) and normotensive pregnancies ($n = 10$)	At birth	- Number of EPC in placental/fetal circulation - EPC proliferation, migration and vasculogenesis	Both circulating EPC and cultivated EPC were decreased compared with controls. Preeclampsia EPC were significantly impaired in their proliferation, migration and vasculogenesis capacities. Preeclampsia groups had higher cord blood level of soluble fms-like tyrosine kinase 1 (sFlt-1).	Preeclampsia reduces the number and function of fetal EPC which could be due to increased sFlt-1 levels.
(24)	Cord blood-derived fetal ECFC from PE ($n = 15$) and normotensive pregnancies ($n = 35$)	At birth	- ECFC levels - ECFC angiogenic function	- ECFC level in PE was lower than control. - There was no difference in the ECFC angiogenic function in terms of capillary network formation, endothelial colony formation, proliferative and migratory response.	ECFC level is lower in PE but there is no difference in the ECFC function.

Abbreviations: AKT1, AKT Serine/Threonine Kinase 1; ANGPTL7, Angiopoietin-related protein; ECFC, Endothelial colony forming cells; EPC, Endothelial progenitor cell; FGF2, Fibroblast growth factor 2; HUVEC, Human umbilical vein endothelial cells; miRNA, microRNA; mRNA, Mesengger RNA, PE, Preeclampsia; sFLT-1, Soluble fms-like tyrosine kinase-1; TFRC, Transferrin Receptor; TGFβ1, Transforming growth factor beta 1; TNFα, Tumor necrosis factor α; VEGFA, Vascular endothelial growth factor A.

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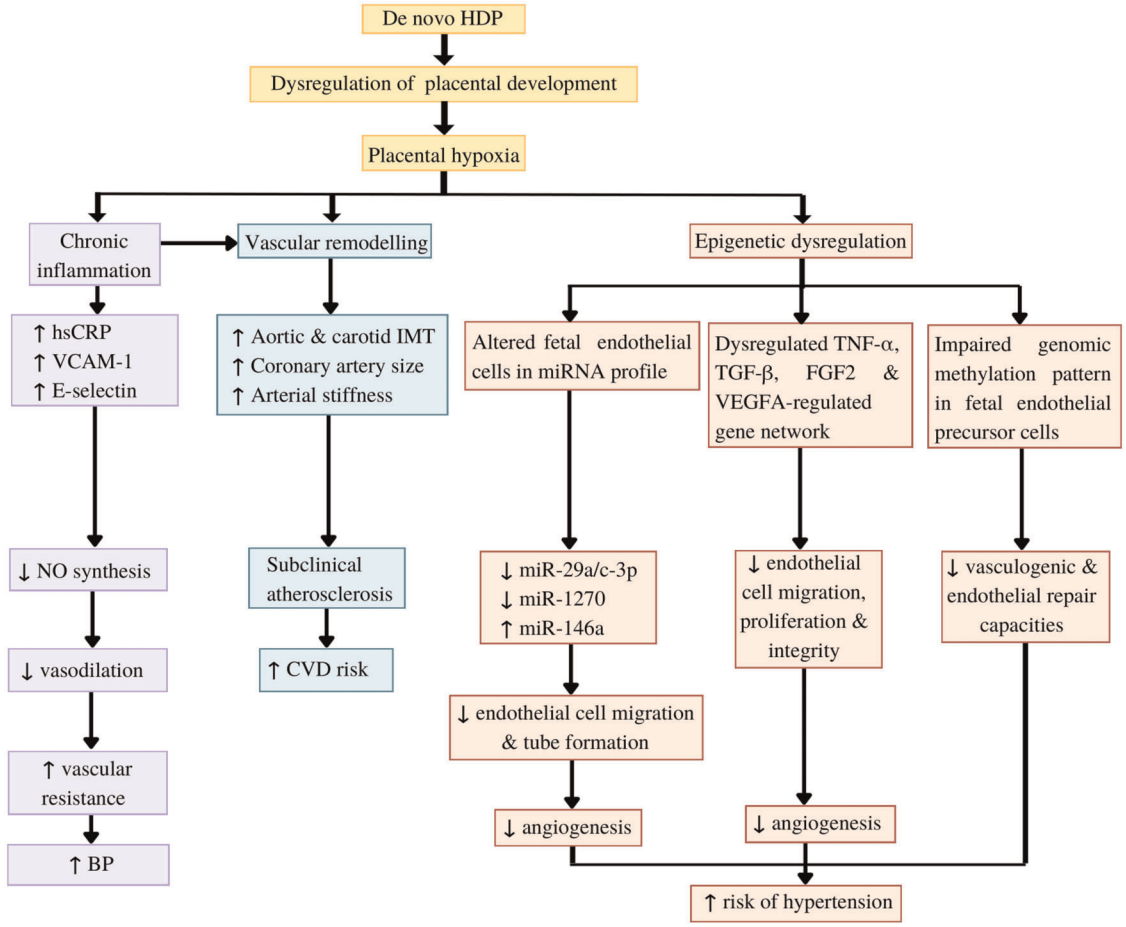

FIGURE 2
Potential mechanisms underlying the impact of *de novo* hypertensive disorders of pregnancy (HDP) on offspring endothelial function. HDP leads to dysregulation of placental development and placental hypoxia. Hypoxia induces chronic inflammation, which inhibits nitric oxide (NO) synthesis, resulting in impaired vasodilatation and increased blood pressure (BP). Both hypoxia and chronic inflammation cause vascular remodelling, which can be detected as subclinical atherosclerotic changes. Furthermore, hypoxia leads epigenetic dysregulation of the offspring endothelial function by causing alteration in the offspring endothelial cells and endothelial precursor cells microRNA (miRNA) profile, dysregulation of several gene networks related to endothelial functions, and impaired genomic methylation pattern in the endothelial precursor cells. These epigenetic dysregulations eventually caused impaired angiogenesis and endothelial repair capacities, which increase the risk of the offspring to develop hypertension (HPT) in later life. CVD: Cardiovascular diseases, FGF2: Fibroblast growth factor 2, hsCRP: high-sensitivity C-reactive protein, IMT: intima-media thickness, TGFβ1: Transforming growth factor beta-1, TNF*α*: tumour necrosis factor α, VCAM-1: vascular cell adhesion molecule 1, VEGFA: vascular endothelial growth factor A.

weeks of gestation (16). This indicates vascular remodelling *in utero* (16). However, whether the increase in carotid IMT in HDP offspring is persistent or temporary is a matter of debate. A 20-year follow up study showed higher carotid IMT in the offspring of HDP (27). However, another study showed that the increase in offspring carotid IMT due to preeclampsia was attenuated at 18 months of life (37). Further studies are needed to address the underlying factors contributing to the difference. In short, *de novo* HDP leads to vascular dysfunction in the offspring by impairing the endothelium-dependent vasodilatation and inducing vascular remodeling such as the subclinical atherosclerosis formation.

HDP promotes endothelial inflammation and dysfunction

In preeclampsia, chronic immune system activation leads to the release of proteins and factors by the placenta. This is part of the inflammatory response that promotes hypertension and proteinuria (38). The factors released include pro-inflammatory cytokines such as hsCRP and TNF-α, which have been reported to be elevated in mothers with preeclampsia (39). The human placenta secretes TNF-α under hypoxia-reoxygenation conditions *in vitro* (40), mimicking the fluctuation of oxygen levels observed in preeclampsia. TNF-α

induces the expression of inflammatory cytokines such as interleukin (IL)-6, IL-8 and monocyte chemotactic protein (MCP-1) and the cellular adhesion molecules including VCAM-1, intercellular adhesion molecule 1 (ICAM-1), E-selectin and epithelial-cadherin (E-cadherin) (41). Furthermore, preeclampsia dysregulates the inducible nitric oxide synthase (iNOS) signaling, thus implicating higher inflammatory responses which potentially lead to severely impaired endothelial functions (22).

High maternal serum VCAM-1 and E-selectin levels in preeclampsia pregnancies was associated with 60%–70% decrease in NO level in the fetal endothelium (18). NO is a marker of endothelial function that acts as a vasodilator, thus reducing vascular resistance and blood pressure. Studies have shown that inhibition of NO synthesis results in reduced blood flow in human (18, 42, 43), vasoconstriction and increased blood pressure in animal offspring (44). This is further supported by another study that showed the RHI of preeclampsia offspring was reduced even at five to eight years after birth (28). RHI is a non-invasive method to measure endothelial function in which the response is partially mediated by endothelium-derived NO. The findings suggest that inflammatory response in preeclampsia inhibits NO synthesis, thus causing endothelial dysfunction and increased risk of hypertension.

HDP causes epigenetic dysregulation of endothelial functions

Epigenetic plays an important role in the developmental origins of health and diseases, where its modifications would be potential mechanisms of the altered environment to be translated into disease development. MiRNAs are a class of noncoding RNAs that regulate essential cellular functions (45), including endothelial cell proliferation, migration, apoptosis, and angiogenesis (46). Previous studies demonstrated that stress conditions including *in utero* stress exposure and inflammation could alter endothelial miRNAs expression (20, 21, 47).

The altered miRNAs expression in *de novo* HDP impacts fetal endothelial functions through gene dysregulation of many signaling pathways. These include the estrogen signaling pathway (48), TGFβ signaling pathway (49), focal adhesion kinase pathway (50), phosphoinositide-3-kinase-protein kinase B (PI3K-Akt) signaling pathway (51), and also through impairment of VEGFA and FGF2 -stimulated angiogenesis (20). Moreover, the alteration of endothelial miRNAs in preeclampsia is not only associated with impaired endothelial cell function and behavior, but it also disrupts angiogenesis and microvascular development in infants as early as the first three months of life (20, 21). It was postulated that impaired angiogenesis *in utero* and early in life predisposes to hypertension development. However, on the brighter side, it is possible that microRNA modification and manipulation could restore the impaired angiogenesis, hence reducing the risk of the offspring to develop hypertension in later life (21).

An epigenetically modified endothelial precursor cell may influence both normal morphogenesis of endothelial cells *in utero* and postnatal vascular repair capacity, hence contributing to CVD risk in the offspring (25). EPC and ECFC are endothelial precursor cells originating from the bone marrow stem cells and human umbilical cord blood. Upon maturation, they become mature endothelial cells and release pro-angiogenic factors like VEGF and placental growth factor (PlGF), which enhance vasculogenesis and endothelial repair (52). Studies found that the numbers of EPC and ECFC in the offspring of preeclampsia mothers were reduced (23, 24), and the EPC were also found to be more senescent, consequently reducing their functional ability (53, 54). Altered number and function of fetal EPC in preeclampsia were associated with increased arterial stiffness (52), which is a risk factor for CVD. Besides, preeclampsia resulted in a different methylation pattern in fetal ECFC, with several differentially methylated regions identified in vascular-related genes (25). DNA methylation plays a pivotal role in regulating biological processes underlying CVD such as atherosclerosis, inflammation and hypertension (55–57). This suggests that epigenetic modifications in HDP may increase the risk of transgenerational vascular disease (58). Besides, these findings open the opportunity to introduce novel epigenetic targets for further experimental study.

Strengths and limitations of the study

To the best of our knowledge, this is the first article that systematically reviewed current evidence related to the effect of *de novo* HDP on offspring endothelial function. The systematic literature search ensures all relevant articles were identified. Studies involving offspring from the prenatal period until adulthood were included, which enable us to understand the effects of *de novo* HDP on offspring endothelial function at different stages of life. However, the current review is not without its limitations. Only one of the studies involved the offspring of mothers with late onset gestational hypertension, while the rest of the studies did not specify the disease stage (i.e., early, or late). Therefore, comparison on the effect of early onset vs. late onset HDP on the offspring endothelial function could not be made. Comparing the effect of different stages of HDP on the offspring endothelial function is an interesting area to be explored. Furthermore, this review was only focused on human studies, while animal studies were excluded. Since animal studies are important tools for investigating how diseases in pregnancy can affect the

offspring, further reviews that include animal models of hypertension in pregnancy are needed in the future.

Conclusion

De novo HDP has a deleterious impact on offspring endothelial function. This is most likely attributed to impaired vasodilation, subclinical atherosclerosis formation, inflammation, and dysregulated epigenetic modification of endothelial functions. Endothelial dysfunction in the offspring of *de novo* HDP may contribute to their risk of developing CVD in later life. A cohort study involving this group of individuals is beneficial to establish the link between endothelial dysfunction in the offspring of HDP with CVD occurrence in adulthood for prevention and early intervention in the future.

Author contributions

AAH and AU contributed to the framework and design of the manuscript. AU, AA, NM, SZA and AAH drafted the manuscript. AS and SJA contributed to the preparation of tables, figures, and figure legends. AU, AA, SZA, and AAH critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The research frontier of cesarean section recovery: A bibliometric analysis

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Background: Cesarean section (CS) has become an effective means to solve dystocia and some obstetric complications, and to save the lives of women and perinatal women. Disparities in quality obstetric care and rehabilitation in CS result from differences in health care systems across regions, and more scientific and reasonable rehabilitation programmes and management measures will benefit more parturient and newborns worldwide who must take CS. In this study, we performed a bibliometric analysis to collect a graphical representation of the CS recovery.

Methods: A total of 995 documents of CS recovery were retrieved from the Web of Science Core Collection (WOSCC) on December 31, 2021, and then VOS viewer 1.6.18 was used for visual analysis.

Results: Over the last 20 years, the researches of CS recovery have gradually increased and it will continue to grow in the next period. Anesthesia and Analgesia is the most popular journal in CS recovery. Most of the representative achievements are concentrated in the relevant institutions of European and American countries, Brendan Carvalho and Ian J. Wrench are among the outstanding scholars in this field, but the overall outcome is limited by limited regional work and lack of broad cooperation and representation. "CS," "surgery," "management," "recovery," "enhanced recovery," and "risk factors" are high frequency keywords, and there is a close relationship between "management" and "enhanced recovery" around the CS and they also become one of the key factors to regulate the condition of patients.

Conclusion: This work firstly analyzed the research condition of CS recovery by a bibliometric analysis. According to the practice guideline, it produces some outstanding representative productions, which involves enhanced recovery after surgery (ERAS) and will continue to be the focus of researchers. More substantive research articles and large-scale clinical studies may greatly enhance the scientific value, and it is necessary to strengthen the ERAS guideline and cooperation between researchers, generate broader consensus and results, and ultimately provide help for CS recovery.

KEYWORDS

cesarean section (CS), recovery, enhanced recovery after surgery (ERAS), bibliometric analysis, Web of Science

Background

Cesarean section (CS) is an important operation in obstetrics. Due to the advances in the knowledge of anesthesiology, blood transfusion, infusion, water and electricity balance, as well as the improvement of surgical methods, surgical suture materials and infection control measures, CS has become an effective means to solve dystocia and some obstetric complications, and to save the lives of women and perinatal women (1). Some data show that CS rates have increased by nearly 50% in the last 20 years (1, 2). In developed countries, CS rates are at their peak. In most developed countries, CS rates are around 30%, due to maternal factors such as advancing age and obesity, as well as medical developments that have made CS safer in terms of maternal and foetal morbidity and mortality (2, 3). In present-day obstetrics, cesarean delivery occurs in one in three women in the United States, and in up to four of five women in some regions of the world (3). CS is often considered a simple and safe alternative to natural delivery, but in some cases, it may be technically difficult and thus a health hazard for both mother and foetus (4, 5). As with any procedure, CS is associated with short – and long-term risks, particularly in Settings that lack the facilities or capacity to perform safe surgery or properly treat surgical complications, or where delivery care or repeat CS is not available as a matter of course in subsequent pregnancies (3, 4).

Surgery is a known physiological stress (6), in which preoperative preparation, operation and postoperative rehabilitation are important factors affecting the health of patients and children after cesarean section. Over the past 100 years, advances in CS technology have made it possible to reduce maternal morbidity and mortality. Nevertheless, maternal mortality and morbidity rates among women in developing countries and underdeveloped regions have increased significantly compared with those in developed regions (3). These disparities pose challenges to health care systems and represent inequalities in access to quality obstetric care and rehabilitation from CS. Therefore, to cope with the inequality of medical resources, it is particularly important to carry out rehabilitation work after cesarean section, involving uterine rehabilitation, physical recovery, pelvic floor muscle rehabilitation, scar management, breastfeeding and lactation function, etc. Physical therapy programs in the early stages of CS are effective and valuable for improving the quality and productivity of postnatal care, thereby improving post-delivery well-being and including reducing the amount of medication needed for pain control and improving the recovery of bowel activity (7). The implementation of a protocol of enhanced recovery for elective CS in a level III maternity is application safe and postoperative pain, nausea and vomiting are well managed, which has been involved in reducing adverse outcomes that can slow recovery, resulting in early discharge of patients while maintaining high levels of satisfaction (8). The application of rapid rehabilitation model of multidisciplinary cooperation and traditional Chinese medicine in CS can effectively improve the recovery rate, ensure the analgesic effect, and improve the maternal and infant outcomes, and has higher health and economic benefits, which is worthy of promotion (9, 10). Thus, more scientific and reasonable recovery programmes and management measures will benefit more parturient and newborns worldwide who must take CS.

In this study, we conducted a bibliometric analysis to gather a diagrammatic drawing of CS rehabilitation. Bibliometrics uses public academic literature data to analyze and track the progress of scientific data, reveal the structure of research and its productivity, evaluate the current status and trends of research, and predict the research prospects of a given topic (11, 12). The data will attract the interest and attention of researchers and enterprises in obstetrical department and parturient.

Materials and methods

Study selection

We retrieved all literature data regarding the caesarean section rehabilitation indexed in the Web of Science Core Collection (WOSCC). The term of caesarean section and rehabilitation were detected with MeSH. The documents from 2000 to 2021 (December 31, 2021) were searched, the language type was set to English, and the document type was set to Article and Review. The execution date of strategies was September 10, 2022 and the search terms and strategies used for the WOSCC database are as follow: #1, "Cesarean delivery" OR "Cesarean deliveries" OR "Cesarean section" OR "Caesarean section" OR "Abdominal delivery" OR "Abdominal deliveries" OR "Postcesarean section"; # 2, "Rehabilitation" OR "Recovery" OR "Physical medicine" OR "Physical therapy" OR "Occupational therapy"; # 3, "# 1" AND "# 2"; #4, #3 AND "Article and Review" AND "English."

Data collection

A total of 995 documents were retrieved from WOSCC database, and then the documents were used to make visual analysis ultimately. The title, publication year, authors, country, institution, keywords, journal, citation frequency, and relative citation ratio were analyzed. The 2021 impact factor (IF) of the journals were obtained from the Journal Citation Reports on September 15, 2022.

Statistical analysis

To extract the most common topics, impactful authors and institutions, we chose the keywords and key references and the visualization of collaboration networks were conducted using VOS viewer version 1.6.8 (Leiden University, Leiden, Netherlands). We choose the keywords and key references to predict the research prospect and research hotspot. Keywords and key references were analyzed by VOS viewer. The parameters of the VOS viewer were set as follows: Method (Linlog/modularity).

Results

Publication outputs

There were 995 documents of CS recovery from WOSCC databases database and which were used to make visual analysis ultimately. The count of annual publications from 2000 to 2021 was shown in Figure 1. It is with weak changes from 2000 to 2009, but the overall trend has gradually increased in recent years and it will continue to grow in the next period.

TABLE 2 Top 10 countries/regions on cesarean section recovery.

Rank	Country/ Region	Documents	Citations	Total link strength
1	USA	225	4,940	62
2	China	136	1,178	7
3	UK	96	2,997	72
4	Turkey	65	734	6
5	Australia	38	801	19
6	Canada	36	895	43
7	India	34	246	3
8	Iran	32	296	1
9	Germany	31	1,118	30
10	Japan	31	362	3

Countries/regions and organization

A total of 76 countries/regions and 1,489 organizations participate in 995 productions were analyzed. As shown in Table 1, USA (n = 225) is the most productive countries and is well ahead of other countries. China, UK, Turkey, Australia, Canada, India, Iran, Germany, and Japan are the other productive countries of the top 10 institutions (Table 2).

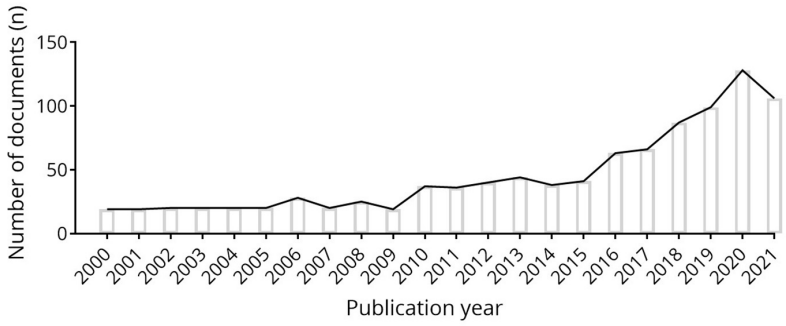

FIGURE 1
Annual number of documents indexed in the WOSCC from 2000 to 2021 by the online bibliometric analysis.

TABLE 1 Top 10 the most productive organizations.

Rank	Organizations	Country	Documents	Citations	Total link strength
1	Stanford University	USA	18	314	19
2	Duke University	USA	12	111	14
3	University of Michigan	USA	9	131	8
4	Nanjing Medicinal University	China	9	41	5
5	Oregon Health and Science University	USA	8	408	28
6	Washington University	USA	8	336	28
7	Oslo University	Norway	8	355	18
8	University of Helsinki	Finland	8	216	6
9	Harvard Medicinal University	USA	8	91	9
10	Fudan University	China	8	90	7

The citations of USA (n = 4,940) and UK (n = 2,997) are ahead, and UK leads China in both citations and total link strength (Table 2). Table 3 showed the top 10 institutions in terms of publications, mainly come from USA (n = 6), China (n = 2), Norway (n = 1), and Finland (n = 1). The top 4 ranked items by publications are Stanford University (n = 18), Duke University (n = 12), University of Michigan (n = 9), and Nanjing Medicinal University (n = 9), and the top 4 institutions by citations are Oregon Health and Science University (n = 408), Oslo University (n = 355), Washington

TABLE 3 Top 10 with the largest number of publications.

Rank	Journals	Documents	2021 impact factor	2021 JCR partition
1	International Journal of Obstetric Anesthesia	44	3.282	Q2
2	Anesthesia and Analgesia	26	6.627	Q1
3	Medicine	21	10.871	Q3
4	Journal of Maternal Fetal Neonatal Medicine	20	2.323	Q3
5	Journal of Obstetrics and Gynaecology Research	20	1.697	Q4
6	European Journal of Obstetrics Gynecology and Reproductive Biology	16	2.831	Q3
7	BMC Pregnancy and Childbirth	15	3.105	Q2
8	Obstetrics and Gynecology	15	7.623	Q1
9	American Journal of Obstetrics and Gynecology	13	10.693	Q1
10	Regional Anesthesia and Pain Medicine	13	5.564	Q2

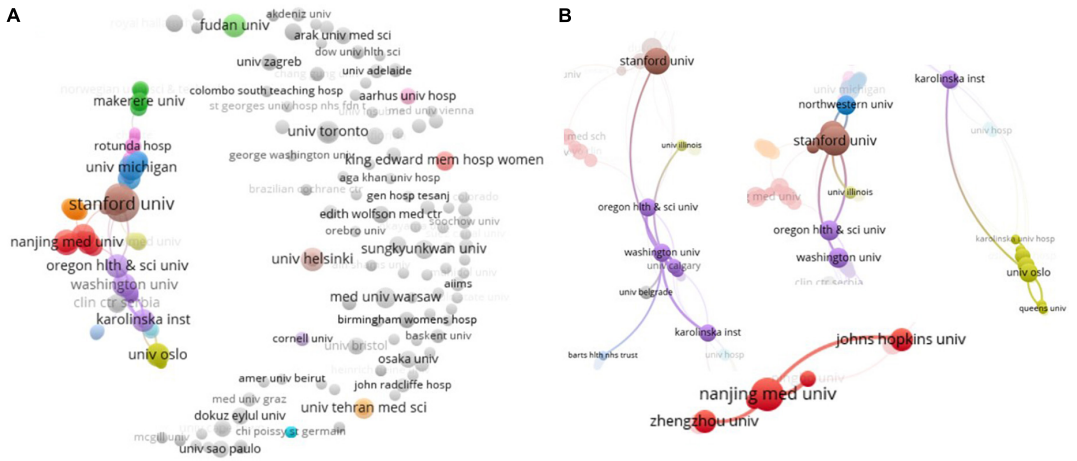

FIGURE 2
Co-author analysis of organizations with network visualization. **(A)** The largest set of 308 valid items were interlinked. **(B)** Some partners of organizations were performed.

TABLE 4 Top 10 active authors with most documents.

Authors	Organizations	Country	Documents	Citations
Brendan Carvalho	Stanford University	USA	17	313
Ian J. Wrench	University of Sheffield	UK	7	436
Pervez Sultan	University College London Hospital	UK	7	104
Aaron B. Caughey	Oregon Health and Science University	USA	5	327
Gregg Nelson	University of Calgary	Canada	5	299
R. Douglas Wilson	Oregon Health and Science University	USA	5	299
Ashraf S. Habib	University of Minnesota	USA	5	57
Jeffrey Huang	University of Central Florida	USA	4	298
George A. Macones	Washington University	USA	4	303
Carol A. Aschenbrenner	Wake Forest School of Medicine	USA	4	38

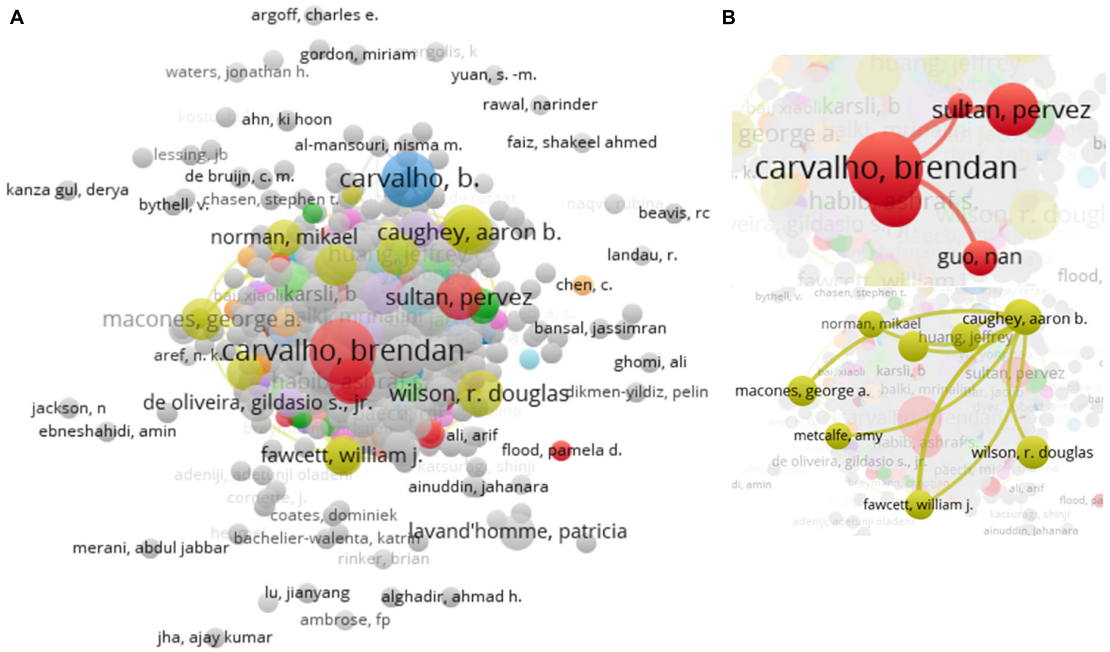

FIGURE 3
Co-occurrence analysis of authors. **(A)** 4,934 items valid items were connected. **(B)** The cooperation of Brendan Carvalho and Aaron B. Caughey were presented.

University (n = 336), and Stanford University (n = 314), but Chinese institutions by publications and citations don't attract much attention (Table 3). According to the statistical analysis, some of the publications are completed in cooperation with multiple institutions and they have cooperation with other institutions (Figure 2). In the network, the largest set of connected items consists of 308 items (Figure 2A). Most of institutions are isolated on the right side, including Fudan University and University of Helsinki. In contrast, Oregon Health and Science University, Washington University, Stanford University, and Oslo University have a wide range of partners (Figure 2B). Although Nanjing Medicinal University has low link strength (Table 3), they have a few good companions (including Zhengzhou University, Johns Hopkins University, etc., Figure 2B).

Journals analysis

In total, 415 journals published research documents related to CS recovery from 2020 to 2021. In Table 4, the top 10 journals are shown that published about 20.40% of documents (203/995). *International Journal of Obstetric Anesthesia* is the most dynamic journal of CS recovery, followed by *Anesthesia and Analgesia*, *Medicine*, *Journal of Maternal Fetal Neonatal Medicine*, *Journal of Obstetrics and Gynaecology Research*, *European Journal of Obstetrics Gynecology and Reproductive Biology*, *BMC Pregnancy and Childbirth*, *Obstetrics and Gynecology*, *American Journal of Obstetrics and Gynecology*, and *Regional Anesthesia and Pain Medicine*. The IF of 10 journals was from 1.697 to 10.693, there are three journal citation reports (JCR) Q1 journals, and *American Journal of Obstetrics and Gynecology* shows the maximum IF of 10.693 (Q1), and *Obstetric Anesthesia* is with IF 3.282 and JCR Q2 (Table 3). According to the documents, IF and JCR partition, *Anesthesia and Analgesia* may be the most popular journal in CS recovery.

Authors analysis

A total of 4,934 authors drafted the 995 documents in CS recovery. In Table 4, the first three most active authors are from the Stanford University (USA), University of Sheffield (UK), and University College London Hospital (UK), Brendan Carvalho is the most active author in CS recovery (with 17 documents and 313 citations), and Ian J. Wrench (University of Sheffield) is the highest citation researcher. Subsequent authors have similar production, but the citations of Ashraf S. Habib and Carol A. Aschenbrenner are weaker (in Table 4). The co-authorship map of all authors was generated (4,934 items, Figure 3A). The connection between authors is loose and most scholars are scattered independently with other activated researchers (Figure 3A). As shown in Figure 3B, the partners of Brendan Carvalho and Aaron B. Caughey are relatively simple and the lack more extensive contacts.

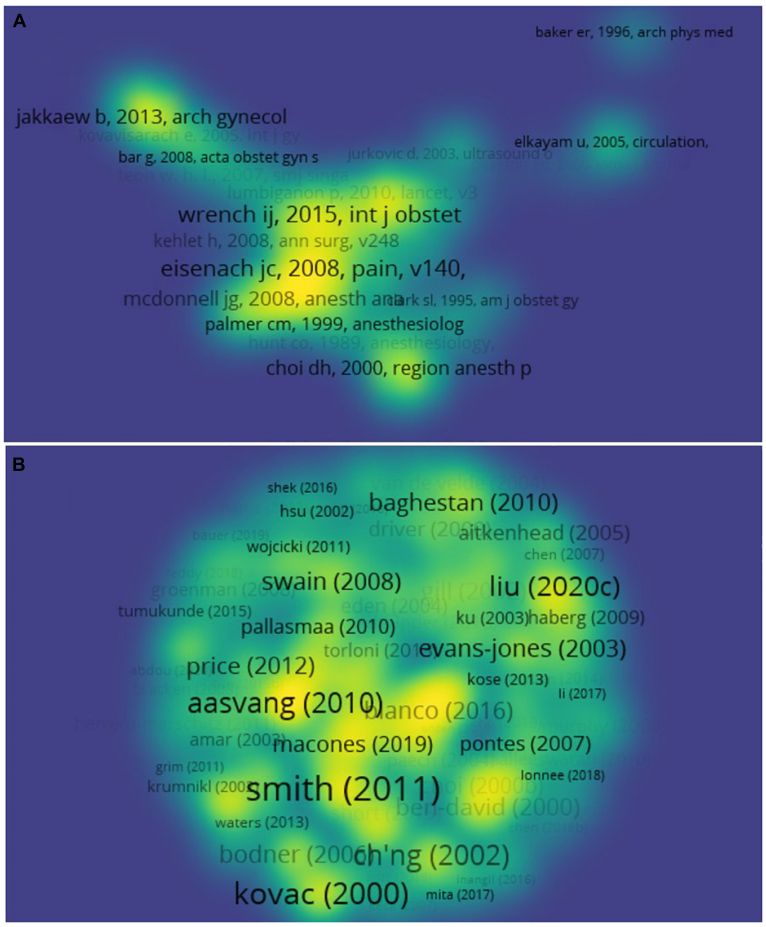

FIGURE 4
Citation analysis of documents. **(A)** The co-citation map of 1,272 cited references was generated. **(B)** The citation map of documents.

Citation analysis

Of the 23,261 cited reference, 1,272 meet the threshold (minimum number of documents of an author: 3) and the co-citation map of cited references was generated (Figure 4A). "Severity of acute pain after childbirth, but not type of delivery, predicts persistent pain and postpartum depression" (13) is the highest cited reference of CS recovery (with 31 citations; Table 5), and it is also the most visible center of the network (Figure 4A). As the practice guideline, "Guidelines for Antenatal and Preoperative care in Cesarean Delivery: Enhanced Recovery After Surgery Society Recommendations (Part 1)," "Guidelines for intraoperative care in cesarean delivery: Enhanced Recovery After Surgery Society Recommendations (Part 2)," and "Guidelines for postoperative care in cesarean delivery: Enhanced Recovery After Surgery (ERAS) Society recommendations (part 3)" are also widely noted, recognized, and cited. In this field, it also produces some outstanding representative productions (Table 6). The top 3 citations of documents are "Perioperative fasting in adults and children: guidelines from the European Society of Anaesthesiology" (review), "Prevention and treatment of postoperative nausea and vomiting" (review), and "Predictive risk factors for persistent postherniotomy pain," and they are also the visible center of the network (article; Table 6 and Figure 4B). The data suggest Ian Smith is very interested in the research of CS recovery, but the researches of Eske K. Aasvang is more important drivers in the development of the field.

Keywords analysis

Of the 3,968 keywords, 1,004 meet the threshold (minimum number of documents of a keyword: 2) and the co-occurrence map of keywords was generated (Figure 5). "CS," "surgery," "management," "recovery," "enhanced recovery," and "risk factors" are high frequency keywords and are also given highlights in the relationship network (Figure 5A). Further analysis reveals a close relationship between "management" and "enhanced recovery" around the CS (Figure 5B), and they also

TABLE 5 Top 10 Co-citation of cited reference.

Rank	Production	First author	Source	Type	Publication year	Total citations
1	Severity of acute pain after childbirth, but not type of delivery, predicts persistent pain and postpartum depression	James C. Eisenach	Pain	Article	2008	31
2	Introduction of enhanced recovery for elective caesarean section enabling next day discharge: a tertiary centre experience	I. J. Wrench	Int J Obstet Anesth	Article	2015	30
3	Guidelines for postoperative care in cesarean delivery: Enhanced Recovery After Surgery (ERAS) Society recommendations (part 3)	George A. Macones	Am J Obstet Gynecol	Review	2019	28
4	Guidelines for Antenatal and Preoperative care in Cesarean Delivery: Enhanced Recovery After Surgery Society Recommendations (Part 1)	R. Douglas Wilson	Am J Obstet Gynecol	Review	2018	28
5	Guidelines for intraoperative care in cesarean delivery: Enhanced Recovery After Surgery Society Recommendations (Part 2)	Aaron B. Caughey	Am J Obstet Gynecol	Review	2018	26
6	The analgesic efficacy of transversus abdominis plane block after cesarean delivery: a randomized controlled trial	John G. McDonnell	Anesth Analg	Article	2008	22
7	Enhanced recovery after elective caesarean: a rapid review of clinical protocols, and an umbrella review of systematic reviews	Ellena Corso	BMC Pregnancy Childbirth	Review	2017	21
8	Effects of gum chewing on recovery of bowel function following cesarean section: a randomized controlled trial	Bordin Jakkaew	Arch Gynecol Obstet	Article	2013	21
9	Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia: a qualitative and quantitative systematic review of randomized controlled trials	J. B. Dahl	Anesthesiology	Article	1999	21
10	Enhanced recovery from obstetric surgery: a U.K. survey of practice	S. Aluri	Int J Obstet Anesth	Article	2014	20

become one of the key factors to regulate the condition of patients.

Discussion

Over the last 20 years, the researches of CS recovery have gradually increased and it will continue to grow in the next period. Anesthesia and Analgesia is the most popular journal in CS recovery. Most of the representative achievements are concentrated in the relevant institutions of European and American countries, Brendan Carvalho and Ian J. Wrench are among the outstanding scholars in this field, but the overall outcome is limited by limited regional work and lack of broad cooperation and representation. According to the practice guideline, it produces some outstanding representative productions, which involves management and enhanced recovery.

Vaginal birth is a natural physiological process, but CS may be necessary to protect the health of the woman and the baby in certain circumstances. In these cases, underuse of CS leads to increased maternal and perinatal mortality and morbidity (14). In contrast, overuse does not show benefits, but may cause harm and waste human and financial resources. On the other hand, failure to obtain a CS in a timely manner can lead to perinatal asphyxia, stillbirth, uterine rupture or obstetric fistula, which is a sign of unusually long obstructed labor (15). Thus, CS should be approached carefully in its testify and aim to make reproductive

TABLE 6 Top 10 citation analysis of documents.

Rank	Title	First author	Source	Type	Publication year	Total citations
1	Perioperative fasting in adults and children: guidelines from the European Society of Anaesthesiology	Ian Smith	Eur J Anaesthesiol	Review	2011	447
2	Prevention and treatment of postoperative nausea and vomiting	A. L. Kovac	Drugs	Review	2000	317
3	Predictive risk factors for persistent postherniotomy pain	Eske K. Aasvang	Anesthesiology	Article	2010	240
4	Prospective study of liver dysfunction in pregnancy in Southwest Wales	C. L. Ch'ng	Gut	Article	2002	232
5	Pregnancy and Perinatal Outcomes of Women With Coronavirus Disease (COVID-19) Pneumonia: A Preliminary Analysis	Dehan Liu	AJR Am J Roentgenol	Article	2020	219
6	Multifactorial preoperative predictors for postcesarean section pain and analgesic requirement	Peter H. Pan	Anesthesiology	Article	2006	181
7	Quadratus Lumborum Block Versus Transversus Abdominis Plane Block for Postoperative Pain After Cesarean Delivery: A Randomized Controlled Trial	Rafael Blanco	Reg Anesth Pain Med	Article	2016	170
8	Catastrophizing: a predictive factor for postoperative pain	Am J. Surg	Am J Surg	Review	2011	165
9	Balloon-assisted occlusion of the internal iliac arteries in patients with placenta accreta/percreta	Leonard J. Bodner	Cardiovasc Intervent Radiol	Article	2006	151
10	Congenital brachial palsy: incidence, causes, and outcome in the United Kingdom and Republic of Ireland	G. Evans-Jones	Arch Dis Child Fetal Neonatal Ed	Article	2003	147

have services accessible to all parturient who need them (15). Optimizing CS use and rehabilitation management is a global concern and public health challenge (4).

Scientific management after CS will be beneficial to rehabilitation. (1) Postoperative monitoring immediately after delivery should be performed in the recovery room, but in special circumstances, it may be performed in the delivery unit, and provided safety rules are maintained and regulators are notified that specific surveillance, including emergency call procedures, must be carried out (16). (2) Systematic blood count immediately after CS is not recommended in the general population. (3) The analgesic regimen developed by the medical team should be appropriate for each patient, and early feeding and drinking under regional or general anesthesia is recommended after elective or emergency CS (17, 18). (4) Indwelling bladder catheter should be inserted before operation and maintained during operation; The bladder catheter should be removed preferentially within 12 h after CS; It is recommended to check for spontaneous urination within 4–6 h after removal of the bladder catheter. If the patient fails to empty within 6 h of extubation, the attending physician should be notified (19–21). (5) Patients are advised and encouraged to get out of bed as early as day 1 (or 6–8 h). (6) Prophylactic treatment with two antiemetics is recommended during CS (22). (7) Whether to add low molecular weight heparin, for obese patients, the dose of low molecular weight heparin needs to be appropriate to body weight (23, 24). (8) Anti-embolic Stockings are recommended for thrombosis prevention on the morning of surgery and for at least 7 days after surgery (16, 25).

ERAS programs are standardized perioperative care plans that, when combined with an audit system and a dedicated multidisciplinary team, can reduce surgical stress, enhance physiological and functional recovery, reduce length of stay, and reduce complications (26, 27). There is increasing evidence to support the success of ERAS for a wide range of surgical procedures, including colorectal, urology, gynecology, and hepatobiliary surgery (27, 28). Then the ERAS principles in obstetrical surgery are also being tried (6, 29). Teigen et al. conduct a randomized controlled trial and reveal that ERAS at CS presents the potential to improve outcomes such as day of discharge is suggested by the observed reduction in overall postoperative length of stay, improved patient satisfaction, and

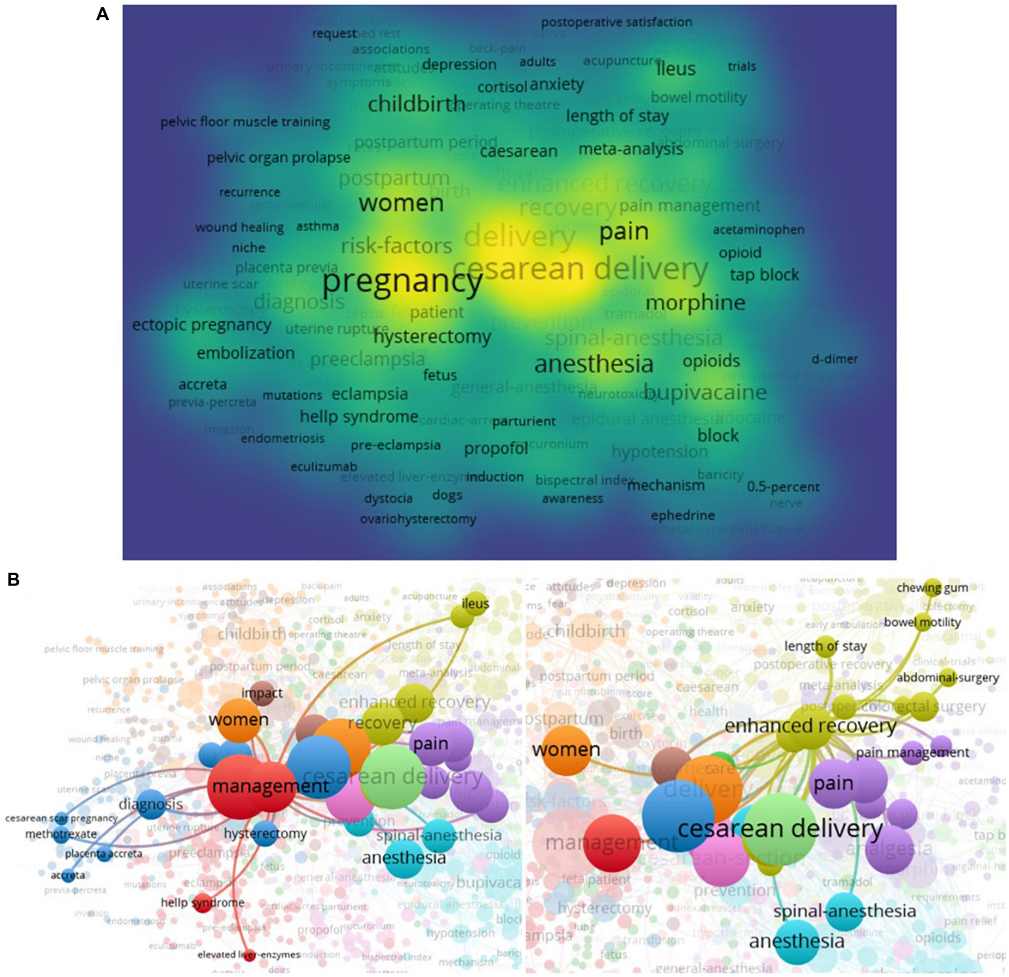

FIGURE 5
Co-occurrence analysis of keywords. **(A)** The network visualization of total keywords (1,004 keywords) was conducted. **(B)** The crosstalk of keywords "management" and "enhanced recovery" were presented.

an increase in breastfeeding rates (30). ERAS also plays an active role in improvement of postoperative pain, intraoperative nausea, hospitalization cost, and patient satisfaction. In a prospective randomized controlled trial, Pan et al. find the ERAS group has significantly fewer patients with intraoperative nausea, pain of visual analog scale (VAS) scores, and VAS grade >3 during rest in the first 24 h and during motion in the first 24 and 48 h after CS; And patient satisfaction rated as per the VAS was significantly higher in the ERAS group (31).

Preliminary studies on the implementation of ERAS after CS have been carried out mainly outside Europe, in which early oral feeding, early mobilization and timely removal of catheter are important components of ERAS, which are mainly performed in patients undergoing scheduled CS (29). In 2017, the ERAS Social Guidelines Committee selected an expert group to review and prepare guidelines for perioperative care of CS. Based on the available evidence in 2017, the recommendations were published in 2018–2019 and are divided into three parts: antenatal and preoperative care, intraoperative care, and postoperative care (32–34). In 2019, the Society of Obstetrical Anaesthesia and Perinatology (SOAP) compiled a consensus document regarding ERAC, which provides recommendations from SOAP on the elements that should be included in ERAS paths, including basic core elements and other recommended elements (17). For the postoperative care, elements include as follow: (1) offer ice chips and water within 1 h postoperatively, consider gum chewing (gum chewing starting right after CS three times a day for about 30 min until the first flatus (35); (2) advance to regular diet within 4 h postoperatively; (3) heparin/saline lock IV once oxytocin infusion complete and tolerating fluids (36); (4) maintain normoglycemia with <180–200 mg/dl; (5) minimize opioid consumption and continue scheduled nonopioid analgesia (37); (6) ambulation should occur soon after motor function returns, beginning with

dangling and out of bed to chair and progressively increasing to 3–4 times after postoperative day 1; (7) removal of urinary catheter 6–12 h postoperatively (early removal of the indwelling urinary catheter in patients who underwent elective CS showed significant less dysuria, less urinary frequency and a decrease in the incidence of significant bacteriuria (20); (8) provide early and robust lactation support (early breastfeeding, adequate sucking stimulation, proper sucking technique, and limited formula may be effective in improving long-term breastfeeding for mothers who have delivered by cesarean section (38); (9) coordinate and streamline discharge processes to facilitate early discharge; (10) limit unnecessary interruptions to maximize rest and bonding. The latest expert consensus also stresses the core outcome, which include compliance with enhanced recovery protocol; fasting times; times to mobilization and urinary catheter removal; provision of optimal analgesia (maternity satisfaction, compliance with analgesia, opioid consumption or requirement and incidence of nausea or vomiting); early breastfeeding success; length of hospital stay; and hospital re-admissions (39). And the outcomes should be considered when designing future enhanced recovery studies.

Due to differences in economic, medical and educational levels, the recent data show CS rates are more than 15% in 63% countries but lower than 10 in 28% countries (1, 40). So, it is important that patients must be educated about the risks of cesarean section as part of pregnancy education, and providers must consider the long-term risks when deciding whether to perform a cesarean section. Educating women about the potential short – and long-term risks of cesarean section to mother and baby is critical to the success of this mission and will also contribute to the medical compliance and effectiveness of rehabilitation management after cesarean section. For the future, the mission continues as we pursue twenty-first century solutions to address alarming rates of obstetric bleeding, perinatal hysterectomies, maternal mortality and unequal resources in health care (3).

Limitations

Some limitations should be addressed in this work. Firstly, the deadline for researched publications was December 31, 2021, but WOSCC would also keep updating, many documents are still being updated in 2022. Besides, the terms of "Cesarean delivery," "Cesarean deliveries," "Cesarean section," "Caesarean section," "Abdominal delivery," "Abdominal deliveries," "Postcesarean section," "Rehabilitation," "Recovery," "Physical medicine," "Physical therapy," "Occupational therapy," "English," "Article" and "Revies" were selected to define the topic of the studies, not all documents were completely obtained, such as the Meeting, Case Report, Clinical Trial, Patent and other multiple document types. Thirdly, because the search was limited to WOS Core Collection databases, some documents MEDLINE®, KCI-Korean Journal Database, and SciELO Citation Index were missed. However, we believe that the overall situation and general trend of these analyses are consistent with the research blueprints of CS recovery.

Conclusion

This work firstly analyzed the research condition of CS recovery by a bibliometric analysis. The data showed CS recovery may be an interesting field of research, but the output and cooperation of more representative works still need to be improved. According to the practice guideline, it produces some outstanding representative productions, which involves ERAS and will continue to be the focus of researchers. More substantive research articles and large-scale clinical studies may greatly enhance the scientific value, and it is necessary to strengthen the ERAS guideline and cooperation between researchers, generate broader consensus and results, and ultimately provide help for CS recovery.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

HW: conceptualization and writing – review and editing. LZ: data collection and analysis and writing – original draft. Both authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Survival and predictors of mortality among preterm neonates in Northern Ethiopia: A retrospective follow-up study

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Background: In the year 2015, more than one-third of neonatal deaths caused by prematurity was recorded worldwide. Despite different kinds of efforts taken at the global and local levels to reduce neonatal mortality, it remains high with low reduction rates, especially in low- and middle-income countries like sub-Saharan Africa and South Asia. Therefore, this study aims to assess the survival status and predictors of mortality among preterm neonates.
Methods: A retrospective follow-up study was conducted on randomly selected 561 preterm neonates. Data were extracted from patient records using a pretested checklist. Data entry and analysis were done using Epi-Data Version 4.4.2.1 and Stata version 14, respectively. The Cox proportional hazard regression model was fitted to identify the predictors of mortality. A hazard ratio with a 95% confidence interval (CI) was estimated and p-values < 0.05 were considered statistically significant.
Result: The proportion of preterm neonatal deaths was 32.1% (180) with an incidence of 36.6 (95% CI: 31.6–42.4) per 1,000 person days. The mean survival time was 18.7 (95% CI: 17.7–19.9) days. Significant predictors for time to death of preterm neonates were respiratory distress syndrome [adjusted hazard ratio (AHR): 2.04; 95% CI: 1.48–2.82], perinatal asphyxia (AHR: 2.13; 95% CI: 1.32–3.47), kangaroo mother care (AHR: 0.14; 95% CI: 0.08–0.24), and gestational age (AHR: 0.85; 95% CI: 0.80–0.90).
Conclusion: Preterm neonatal death is still a major public health concern. Respiratory distress syndrome, perinatal asphyxia, kangaroo mother care, and gestational age were independent significant predictors for time to death, as found in this study. Hence, priority must be given to neonates with the above illnesses and strengthen the management and care of preterm neonates.

KEYWORDS

survival, predictor, mortality, preterm neonate, north, Ethiopia

1. Introduction

Neonatal mortality is a global burden that affects both developing and developed countries. Globally, approximately 2.7 million neonatal deaths were reported in the year 2015, accounting for 45·1% of under-five mortality. Prematurity was responsible for 1.05 million deaths that occurred in under-five children worldwide in 2015, of which 0.356 million deaths occurred in

Abbreviations
ACSH, Ayder comprehensive specialized hospital; AHR, adjusted hazard ratio; ANC, antenatal care; C/s, caesarian section; CHR, crude hazard ratio; CI, confidence interval; CSH, Comprehensive specialized hospital; EDHS, Ethiopian Demographic Health Survey; HIE, hypoxic ischemic encephalopathy; IVH, intraventricular hemorrhage; KMC, kangaroo mother care; NEC, necrotizing enterocolitis; PNA, perinatal asphyxia; RDS, respiratory distress syndrome; SVD, spontaneous vaginal delivery; UNICEF, United Nations International Children's Emergency Fund; UOG, University of Gondar; WHO, World Health Organization.

sub-Saharan Africa (1). In 2010, the leading cause of under-five mortality was infectious disease (64%), and prematurity-related deaths accounted for only 14% (2). Then, after 5 years, prematurity became the second leading cause of under-five mortality (3), and from 2015 until now, prematurity has been the foremost cause of under-five and neonatal mortality (1).

Despite such mortality affecting all countries of the world, there is a difference in terms of survival between developed and developing countries; neonates born in Africa have 12 times high risk of mortality compared with those born in Europe (4). Sub-Saharan Africa has a high neonatal mortality rate (27%) compared with European countries (5%) but has a low annual neonatal mortality reduction rate (2.4%) compared with the global reduction rate (3%) (5).

Preterm neonates who are born before 37 completed weeks of gestation (6) have a high risk of mortality (7, 8) and adverse health outcomes (9). Preterm birth is a major contributor to the loss of human potential (10) and to hospital admission (11). Moreover, preterm neonates who survive after the neonatal period have a high risk of neurodevelopmental and learning impairment, visual disorders, long-term cardiovascular disease, and other non-communicable diseases (12, 13). In 2010, 3.1% of disability-adjusted life years occurred because of prematurity (14).

According to the 2017 United Nations International Children's Emergency Fund (5) report, the neonatal mortality rate in Ethiopia was 27% (5). Furthermore, the 2013 UNICEF report clustered Ethiopia among the top 25 countries with high under-five mortality (3); prematurity was one of the foremost causes (15). In addition, the Ethiopian Demographic Health survey (EDHS) report indicated the trends of neonatal mortality—29% in 2016 (16) and 30% in 2019 (17). Moreover, previous studies conducted in Ethiopia showed a high neonatal mortality rate (18–21) and a low reduction rate (20).

Previous studies identified respiratory distress syndrome (RDS) (19, 22), asphyxia (18, 22, 23), sex (24–27), maternal residency (19, 28), gestational age (25, 29, 30), birth weight (18, 27, 31), neonatal sepsis (19, 23, 26), jaundice (18, 23), hyaline membrane disease (18, 23), hypothermia at admission (23), hypoglycemia (18), maternal chronic disease (19, 22), and parity (22) as a predictor of mortality for preterm neonates.

Although the above predictors have been identified, the mortality of preterm neonates continues to be high and is on an increasing trend. Furthermore, if Sustainable Development Goal 3 is to be achieved by the year 2030, conducting relevant studies on crucial topics such as neonatal mortality is essential. Such studies will also support the realization of the goal of the National Newborn and Child Survival Strategy. Therefore, this study aims to assess the survival status and predictors of mortality among preterm neonates in Northern Ethiopia.

The results of this study will help program planners, decision makers, and implementers to know the gaps in current practices of preterm neonate management, focus on the identified gaps, and take action.

2. Methods and materials

2.1. Study area and design

An institution-based retrospective follow-up study was conducted in comprehensive specialized hospitals in the Tigray region. The Tigray region is one of the nine federal administrative regions in Ethiopia. It covers an estimated area of 41,409.95 km^2 with the capital city of Mekelle, which is approximately 781 km away from Addis Ababa, the capital city of Ethiopia. The region has an estimated total population of 5,377,144, with 2,651,167 (49.3%) males and 2,725,977 (50.7%) females. Among the total population, 159,164 are under -1-year infants. There are 2 comprehensive specialized hospitals, 15 general hospitals, 23 primary hospitals, 245 health centers, and 750 health posts in the Tigray region (32). This study was conducted in these comprehensive specialized hospitals.

The Ayder comprehensive specialized hospital (ACSH) has 45 neonatal beds in the neonatal intensive care unit (NICU) and more than 170,000 patient flows per year. The Aksum comprehensive specialized hospital provides its service to a population of over 3.6 million from the central, northwest, and western zones of the Tigray regional state. It has a total capacity of 173 beds, including 13 neonatal beds. In both hospitals, intubation, vasopressors, IV antibiotics, and gavage feeding are offered.

2.2. Population

In this study, the target population was all preterm neonates who were treated in the two comprehensive specialized hospitals of the Tigray region. Preterm neonates who were treated in the ACSH and Aksum comprehensive specialized hospital between February 1, 2017, and January 30, 2019, constituted the study population.

2.3. Eligibility criteria

Preterm neonates (born before 37 completed weeks of gestation) who were admitted to the ACSH and Aksum NICUs between February 1, 2017, and January 30, 2019, were included in this study. Preterm neonates who had incomplete medical records relating to the mainly required variables (date of birth, date of admission, outcome status, and date at which outcome was determined) were excluded.

2.4. Sample size determination and sampling technique

The required sample size for this study was determined by using the Stata statistical package (Cox model), version 14, and the following assumptions: a hazard ratio (HR) of 1.55 for selected covariate of interest (perinatal asphyxia, PNA) from a study done in Gondar, Ethiopia (18), a variability (SD) of 0.5, a probability of failure (death) of 0.288 (18), a margin of error of 5%, and a confidence interval (CI) of 95% to achieve 80% power. After the addition of a 5% non-response rate, the final sample size for this study was 597. A simple random sampling technique was employed. The required number of subjects were proportionally allocated for both hospitals based on their population size (**Figure 1**).

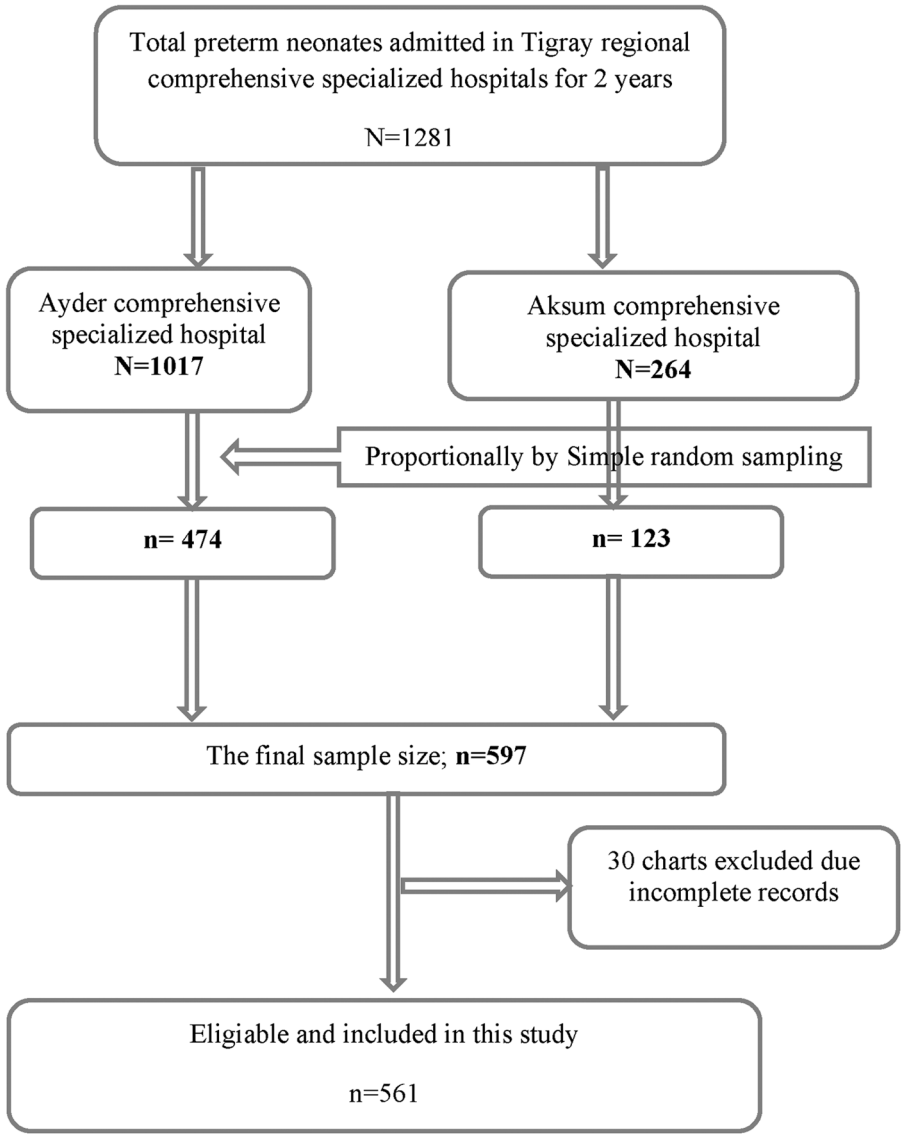

FIGURE 1
Flow diagram of study participants.

2.5. Operational definitions and measurements

The date of admission was the initial follow-up time and the follow-up was done on 28 days of life.

2.5.1. Survival time

The time from admission to the event (death).

2.5.2. Event

Death of preterm neonates after admission to the NICU.

2.5.3. Time scale

The survival time was measured in days.

2.5.4. Censored

Preterm neonates who were discharged after recovery, lost to follow-up, subjected to parental refusal to medical advice, transferred to other health institutions, and remained in the NICU after 28 days were considered censored.

2.5.5. Congenital anomalies

In this study, congenital anomalies represent neural tube defects, encephalocele, anencephaly, duodenal and choanal atresia, cleft lip and palate, and gastroschisis (33).

2.5.6. Respiratory distress syndrome

This condition is characterized by grunting while breathing, rapid or shallow breathing, and flaring of the nostrils (34).

2.5.7. Apnea of prematurity

Respiratory pauses >20 s or pauses <20 s that are related to bradycardia (<80 beats/minute), central cyanosis, and/or oxygen saturation <85% in neonates born at <37 gestation weeks and without causal disorders that induce apnea (34).

Perinatal asphyxia: an Apgar score that remained at less than 7 (at 5 min after birth) and evidence of acute hypoxic compromise with acidemia (35).

2.5.8. Neonatal jaundice

This is defined as elevated total serum bilirubin (TSB) and clinically manifests as a yellowish discoloration of the skin, sclera, and mucous membrane.

2.6. Data collection tool and procedures

The data were extracted from the medical records of preterm neonates who were admitted to the NICUs. A pretested checklist adapted from a study done in Addis Ababa, Ethiopia (36), was used for data collection. After permission was obtained from both hospitals, the list was prepared by investigators based on the information obtained from the NICU health management system registration book. Then, the data were scouted by some select people in this study. Finally, to fill the checklist, all obtained medical records were assessed by data collectors with supervision.

2.7. Data quality control

A pretest was conducted on 5% of the sample size in Mekelle general hospital. Data were collected by two trained and experienced diploma nurses and four BSc nurses, and two master's students acted as supervisors. During the data collection period, a close follow-up, monitoring, and guidance were carried out. The completeness and consistency of the data were checked daily. Before the entry of data, the checklist was patterned for tracking errors and a checklist that contained errors was excluded from the analysis.

2.8. Data processing, analysis, and presentation

The data were coded and entered by using Epi-Data manager version 4.4.2.1 and transferred to Stata statistical software version 14 for clearance and analysis. The Cox proportional hazard regression model was used. After Cox proportional hazard regression was done for each variable, a variable with a p-value <0.25 was entered for multivariate analysis. Multicollinearity was checked by using the variance inflation factor. The Cox proportional hazard regression assumption was tested by using the Schoenfeld residual test (global test). The overall goodness of model fitness was checked graphically by using the Cox Snell residual graph (**Supplementary Annex S1**). The overall model adequacy was checked through Harrell's C test. Lastly, after multivariate analysis, an association was expressed through the hazard ratio and statistically significant predictors were identified using 95% CI and p-value. The results of this study were presented by way of tables, texts, and graphs.

2.9. Ethics approval and consent to participate

The study protocol was evaluated and approved by the Institution of Review Board (IRB) of the College of Health Sciences, Mekelle University, and ethical clearance was obtained. A letter of cooperation was written to the chief executive managers of the ASCH and Aksum comprehensive specialized hospital. The hospital managers provided the right to access the chart of neonates. Finally, confidentiality and anonymity of the data were secured.

3. Result

3.1. Sociodemographic predictors

In this study, out of 597 preterm neonate medical charts, only 561 were complete and were included, with a 94% response rate. Out of the 561 preterm neonates, 444 (79.1%) were admitted to the ACSH, and of these, 140 (31.5%) died. Approximately 310 (55.3%) preterm neonates were males; among these, 98 (31.6%) died. Only 26 (4.6%) preterm neonates were born at home, and 12 (46.1%) of these died. A total of 406 (72.4%) moderate-to-late preterm neonates were born; among these, 95 (23.4%) died. The median gestational age at birth was 33 weeks and 6 days (IQR: 31 weeks and 3 days, 35 weeks). The median maternal age was 26 with an IQ of (22, 30) years (**Table 1**).

3.2. Neonatal-related predictors

In this study, 344 (61.3%) preterm neonates had a birth weight between 1,500 and 2,500 g; 72 (20.9%) died. A total of 191 (34%) preterm neonates did not receive any feeding after delivery; 127 (66.5%) of these died. Moreover, 375 (66.8%) babies did not receive kangaroo mother care (KMC). Of these, 166 (42.3%) died. The Apgar score of 386 (68.8%) babies was known at birth. Among these, the median Apgar score at the 1st and 5th minute were 7 (IQR: 2) and 8 (IQR: 2), respectively (**Table 2**).

3.3. Preterm birth–related predictors

Only 41 (7%) preterm neonates did not have medical and surgical complications. Among those who had such complications, 227 (40.5%), 378 (67.4%), 13 (2.3%), and 12 (2.1%) of them had RDS, sepsis, thrombocytopenia, and necrotizing enterocolitis (NEC), respectively (**Table 3**).

TABLE 1 Distribution of sociodemographic and obstetric-related characteristics in Northern Ethiopia, 2022 ($n = 561$).

Characteristics	Survival status		Percentage
	Death	Censored	
Place of admission			
Aksum Hospital	40	77	20.9
Ayder Hospital	140	304	79.1
Sex			
Male	98	212	55.3
Female	82	169	44.7
Place of delivery			
Home	12	14	4.6
Health center	20	46	11.8
Hospital	148	321	83.6
Gestational age in weeks			
Less than 32	85	70	27.6
Between 32 and 37	95	311	72.4
Neonatal age at admission			
Less than 24 h	170	346	92
Between 1 and 7 days	10	28	6.8
7 days and above	-	7	1.2
Residency			
Urban	96	213	55.1
Rural	84	168	44.9
Maternal age in year			
Less than 20	14	32	8.2
Between 20 and 34	148	294	78.8
35 and above	18	55	13
Parity of the mother			
Less than 2	81	200	50.1
Between 2 and 4	80	136	38.5
5 and above	19	45	11.4
Antinatal care visit			
Yes	174	372	97.3
No	6	9	2.7
Maternal corticosteroid intake			
Yes	16	65	14.4
No	164	316	85.6
Maternal hypertension			
Yes	6	13	3.4
No	174	368	96.6
Maternal sero-status			
Positive	5	13	3.2
Negative	175	368	96.8
Obstetric complications			
Yes	43	103	26
No	137	278	74
Pregnancy type			
Single	114	227	60.8
Multiple	66	154	39.2
Mode of delivery			
SVD	142	285	76.2
C/S	32	91	21.9
Instrumental	6	5	1.9
Presentation at delivery			
Cephalic	150	315	82.9
Noncephalic	30	66	17.1

SVD, spontaneous vaginal delivery; C/s, caesarian section.

3.4. Maternal- and obstetric-related predictors

Out of 561 preterm neonates, 50% were born to mothers who had a parity of less than 2, and 546 (97.3%) were born to mothers who had antenatal care (ANC) follow-up. A total of 460 (86.2%) babies were born to mothers who had three and more ANC visits. A majority (85.6%) of preterm neonates were born to mothers who had not taken corticosteroids before delivery; of these, 164 (34.2%) died. A total of 146babies (26%) were born to mothers who had obstetric complications; among these, 40 (27.4%) were born to those who suffered antepartum hemorrhage (Table 1).

3.5. Overall survival function

According to Kaplan–Meier survival estimates, 160 (88.9%) deaths occurred in the first week of admission, of which 53 (33.1%) died within the first 24 h of admission. In this study, the survival function vs. survival time was a decreasing step function (Figure 2). The survival probabilities for preterm neonates at the end of the first day, 7th day of admission, 14th day of admission, 21 days, and at the end of 28 days of admission were 90.5%, 67.7%, 62.8%, 60.4%, and 56.4%, respectively. Kaplan–Meier survival function estimation graphs were prepared for categorical covariates to observe survival differences (Figure 3).

TABLE 2 Distribution of neonatal-related characteristics for preterm neonates in Northern Ethiopia, 2022 ($n = 561$).

Characteristics	Survival status		Percentage
	Death	Censored	
Birth weight in grams			
2,500 and above	5	41	87.8
Between 1,500 and 2,500	72	344	79.1
Between 1,000 and 1,500	82	153	46.4
Less than 1,000	21	23	8.7
Received kangaroo mother care			
Yes	14	186	35.6
No	166	375	64.4
Weight for gestational age			
Small	21	43	11.3
Appropriate	159	333	87.7
Large	–	5	0.89
APGAR score at birth			
Known	120	266	68.9
unknown	60	115	31.1
Having congenital anomalies			
Yes	2	14	2.8
No	178	367	97.2
Neonates with respiratory distress syndrome			
Yes	116	111	40.5
No	64	270	59.5
Neonatal jaundice			
Yes	21	44	11.6
No	159	337	88.4
Hypoglycemia diagnosed at admission			
Yes	8	50	10.3
No	172	331	89.7
Hypothermia diagnosed at admission			
Yes	78	172	44.5
No	102	209	55.5
Neonates with clinically diagnosed perinatal asphyxia			
Yes	19	12	5.5
No	161	369	94.5
Neonates with clinically diagnosed sepsis			
Yes	133	245	67.4
No	47	136	32.6
Newborns with anemia			
Yes	5	14	3.4
No	175	367	96.6
Newborns diagnosed with thrombocytopenia			
Yes	8	5	2.3
No	172	376	97.7
Newborns with apnea of prematurity			
Yes	16	8	4.3
No	164	373	95.7
Neonates with necrotizing enterocolitis			
Yes	9	3	2.1
No	171	378	97.9

(*continued*)

TABLE 2 Continued

3.6. Survival status of preterm neonates

In this study, 180 (32.1%) preterm neonates died during the follow-up period (**Figure 4**). The median length of follow-up was 6 days. The total person-day-observations were 4,917 days. The overall incidence of mortality for preterm neonates was 36.6 (95% CI: 31.6, 42.4) per 1,000 person days. Furthermore, the overall mean survival time of preterm neonates was 18.8 (95% CI: 17.7–19.9) days.

3.7. Predictors for time to death of preterm neonates

Bivariable and multivariate Cox proportional hazard regression were fitted to identify predictors for the time to death of preterm neonates. Variables that had a p-value <0.25 in the bivariable analysis were entered into the multivariate analysis. Findings from the bivariable analysis showed that respiratory distress syndrome, birth weight, apnea of prematurity, anemia, perinatal asphyxia, kangaroo mother care, congenital anomalies, gestational age, maternal corticosteroid intake, and hypoglycemia at admission were significantly associated with the time to death of preterm neonates. Before multivariate analysis, the global test was checked and it did not violate the assumption; the overall global test = 0.53. The model adequacy test (Harrell's C test) was 0.8 (80%). Multicollinearity was checked by VIF and it was 1.1. In multivariate analysis, four variables, respiratory distress syndrome, perinatal asphyxia, gestational age, and kangaroo mother care, were identified as independent predictors for the time to death of preterm neonates.

TABLE 3 Bivariable and multivariate Cox proportional hazard regression output for predictors to the time to death of preterm neonates in Northern Ethiopia, between February 1, 2017, and January 30, 2022 ($n = 561$).

Variables	Categories	Survival status		CHR (95% CI)	AHR (95% CI)
		Death	Censored		
Kangaroo mother care	Yes	14	172	0.12 (0.07–0.21)	0.14 (0.08–0.24)**
	No	166	209	1	
Gestational age	–			0.79 (0.74–0.84)	0.85 (0.80–0.90)**
Maternal corticosteroid exposure	Yes	16	65	1	
	No	164	316	1.76 (1.05–2.93)	1.18 (0.70–2.00)
Respiratory distress syndrome	Yes	116	111	2.65 (1.96–3.60)	2.04 (1.48–2.82)**
	No	64	270	1	
Perinatal asphyxia	Yes	19	12	2.46 (1.52–3.96)	2.13 (1.32–3.47)*
	No	161	369	1	
Anemia	Yes	3	14	0.42 (0.13–1.31)	0.38 (0.12–1.21)
	No	177	367	1	
Apnea of prematurity	Yes	16	8	2.14 (1.28–3.58)	1.45 (0.85–2.47)
	No	164	373	1	
Hypoglycemia	Yes	78	172	0.49 (0.24–0.99)	0.94 (0.45–1.95)
	No	102	209	1	
Congenital anomalies	Yes	2	14	0.36 (0.09–1.47)	1.76 (0.43–7.18)
	No	178	367	1	

CHR, crude hazard ratio; AHR, adjusted hazard ratio.
*Significant (p-value < 0.01).
**Significant ($p < 0.05$).

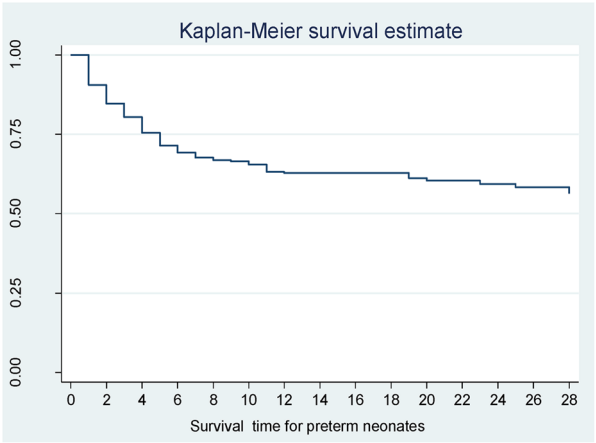

FIGURE 2
Overall survival function for preterm neonates in Northern Ethiopia, between February 1, 2017, and January 30, 2022 ($n = 561$).

Preterm neonates having respiratory distress syndrome were twice [adjusted hazard ratio (AHR): 2.04; 95% CI: 1.48–2.82] more likely to die compared with their counterparts. Neonates having perinatal asphyxia were twice (AHR: 2.13; 95% CI: 1.32–3.47) more likely to die compared with their counterparts in the comparison group. As the gestational age increased in 1 week, the death rate decreased by 15% (AHR = 0.85; 95% CI: 0.80–0.90). Preterm neonates who received kangaroo mother care were 86% (AHR: 0.14; 95% CI: 0.08–0.24) less likely to die compared with their counterparts (Table 3).

4. Discussion

This study aimed to assess the survival status and predictors of mortality among preterm neonates admitted in the comprehensive specialized hospitals located in Northern Ethiopia, Tigray region. The incidence of mortality and the mean survival time for preterm neonates were 36.6 (95% CI: 31.6–42.4) per 1,000 person-day-observations and 18.8 days, respectively. RDS, PNA, KMC, and gestational age were identified as independent significant predictors for the time to death of preterm neonates.

The mean survival time of preterm neonates was lower than that in a study done in the University of Gondar (UOG) comprehensive specialized hospital, Ethiopia, which was 20.4 (22). This difference might be due to a high mortality rate in this study. Furthermore, the mean survival time of preterm neonates in this study was also lower than that in a study conducted in Iran, which was 43.0 (29). This variation might be due to differences in the length of follow-up. In a study conducted in Iran, preterm neonates were followed up until discharge with a maximum hospital stay of 105 days. However, in this study, neonates were followed up until 28 days,

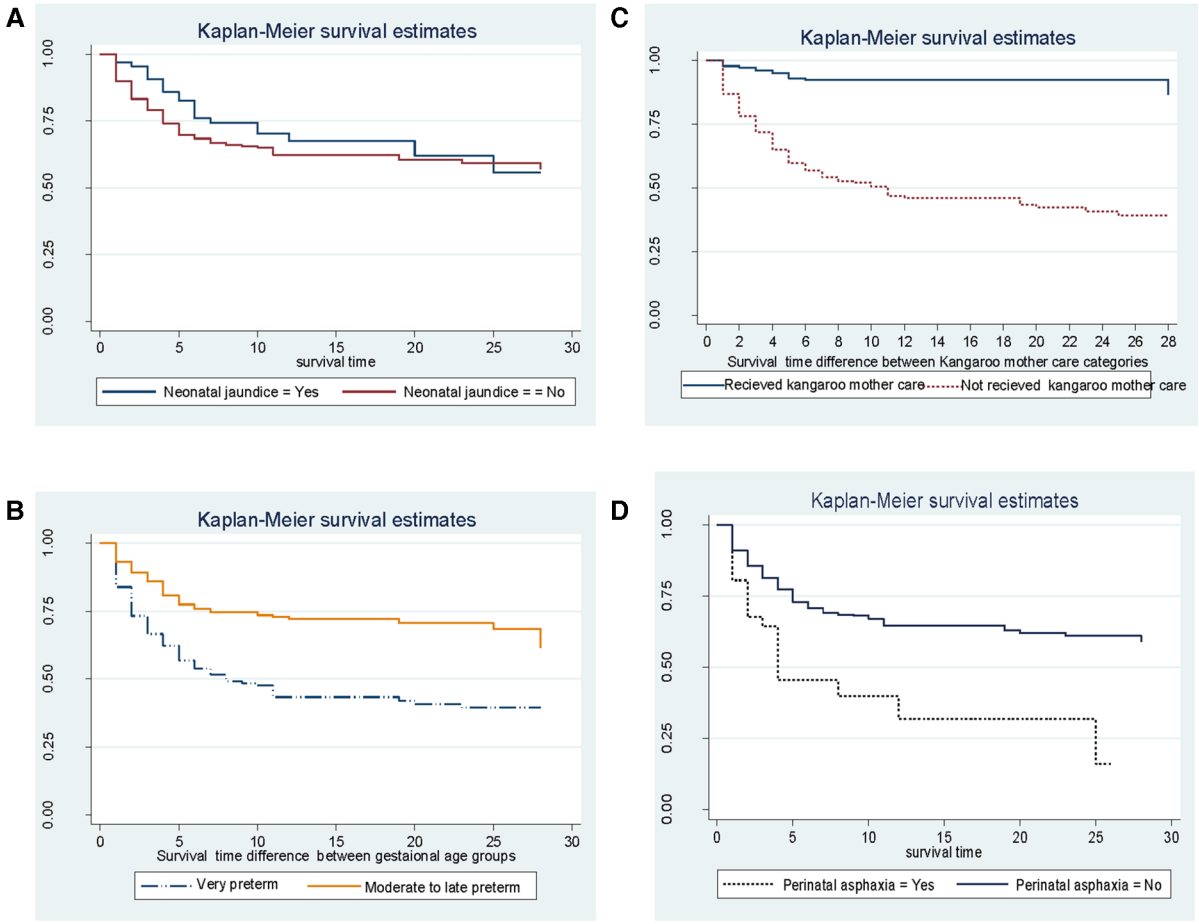

FIGURE 3
Kaplan–Meier estimated survival difference for selected covariates (A–D) of preterm neonates in Northern Ethiopia, between February 1, 2017, and January 30, 2019, and 2022 (n = 561).

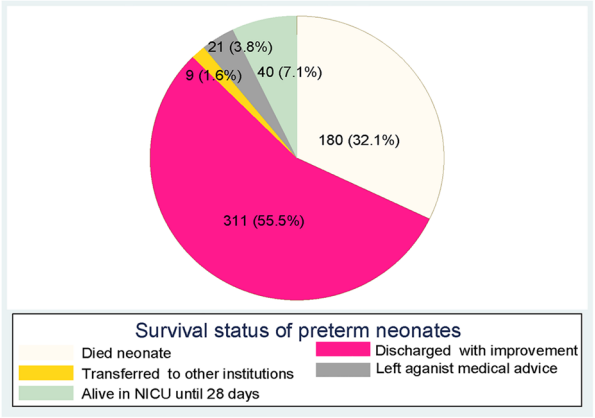

FIGURE 4
Survival status of preterm neonates at the end of follow-up in Northern Ethiopia, between February 1, 2017, and January 30, 2019, and 2022 (n = 561).

which made the survival time lower than that in the above study finding.

Preterm neonates who had RDS during hospital stay had increased hazards or risks of death compared with their counterparts. This finding was in line with a study conducted at Jimma University specialized hospital in Ethiopia (23). Another study that was conducted in Ethiopia also supported this finding (22). These study agreements might be attributed to the fact that the main cause of respiratory distress syndrome in preterm neonates is hyaline membrane deficiency, and preterm neonates who have RDS mostly develop acute complications such as pulmonary hemorrhage, apnea of prematurity, and intraventricular hemorrhage (IVH), which increase the risk of mortality (37).

Neonates who had perinatal asphyxia were more likely to die compared with their counterparts. This finding was consistent with that of studies done at the UOG comprehensive specialized hospital (18, 22) and Jimma University specialized hospital (23). This similarity might be attributed to the same levels of quality care provision for asphyxiated preterm neonates because all hospitals were comprehensive specialized hospitals. Also, perinatal asphyxia is one of the leading causes of neonatal mortality in Ethiopia (16), and perinatal asphyxia has the potential to cause damage to all organs of the body, including the brain and kidneys, and to impair gas exchange, in addition to causing organ immaturity in preterm neonates that facilitates neonatal mortality. Moreover, this similarity might be attributed to perinatal asphyxia causing severe complications such as hypoxic ischemic

encephalopathy (HIE) and IVH, which have a high level of incidence in preterm neonates (15).

Preterm neonates who received KMC had less risks of mortality, and this result was similar to that of the study conducted in the UOG comprehensive specialized hospital (18). This similarity might be due to the majority of preterm neonates not receiving kangaroo mother care, as found in both studies, and KMC also protects neonates from infection, effectively treat hypothermia, improve gastrointestinal function and cardiorespiratory stability, and initiate/encourage breastfeeding. One systematic review and meta-analysis also supported this finding (38). In view of the important benefits of KMC, the World Health Organization (WHO) has strongly recommended its use as a package to treat preterm neonates (39).

In this study, as noted previously, it was found that when the gestational age increased by 1 week, the risk of mortality decreased by 15%. This finding was in line with that of a study conducted at the University of Gondar, Ethiopia (18). Also, this finding was supported by studies conducted in Ethiopia (23), Iran (29), and East Africa (30). Clinical evidence also supports this finding. The link between gestational age and mortality could be traced to the fact that organ immaturity leads to higher mortality; the more preterm, the more organ immaturity.

Because of the retrospective nature of the study design, an incomplete recording of data was a major limitation of this study.

5. Conclusion

The incidence of preterm neonatal mortality was high in this study. The most critical period for preterm neonatal mortality was the first week of admission, especially the first 24 h. The mean survival time of preterm neonates in this study was found to be lower than that in previous studies. Respiratory distress syndrome, perinatal asphyxia, gestational age, and kangaroo mother care were identified as predictors for the time to death of preterm neonates. To decrease the risk of mortality, health professionals should strengthen their follow-up regimens for very preterm neonates and neonates who have PNA and RDS. Moreover, health professionals should make the implementation of kangaroo mother care more stringent, since our study was retrospective study institutional related factors were not assessed. Therefore, we recommend prospective studies.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Institution of Review Board (IRB) of the College of Health Sciences, Mekelle University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

BG conceptualized the study, wrote the proposal, and performed data analysis and manuscript preparation. HB, FM, and JN supervised subsequent drafts of the paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.1083749/full#supplementary-material.

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Pooled prevalence and determinants of antenatal care visits in countries with high maternal mortality: A multi-country analysis

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Background: Complications during pregnancy and childbirth are the leading causes of maternal and child deaths and disabilities, particularly in low- and middle-income countries. Timely and frequent antenatal care prevents these burdens by promoting existing disease treatments, vaccination, iron supplementation, and HIV counseling and testing during pregnancy. Many factors could contribute to optimal ANC utilization remaining below targets in countries with high maternal mortality. This study aimed to assess the prevalence and determinants of optimal ANC utilization by using nationally representative surveys of countries with high maternal mortality.

Methods: Secondary data analysis was done using recent Demographic and Health Surveys (DHS) data of 27 countries with high maternal mortality. The multilevel binary logistic regression model was fitted to identify significantly associated factors. Variables were extracted from the individual record (IR) files of from each of the 27 countries. Adjusted odds ratios (AOR) with a 95% confidence interval (CI) and *p*-value of $\leq$0.05 in the multivariable model were used to declare significant factors associated with optimal ANC utilization.

Result: The pooled prevalence of optimal ANC utilization in countries with high maternal mortality was 55.66% (95% CI: 47.48–63.85). Several determinants at the individual and community level were significantly associated with optimal ANC utilization. Mothers aged 25–34 years, mothers aged 35–49 years, mothers who had formal education, working mothers, women who are married, had media access, households of middle-wealth quintile, richest household, history of pregnancy termination, female household head, and high community education were positively associated with optimal ANC visits in countries with high maternal mortality, whereas being rural residents, unwanted pregnancy, having birth order 2–5, and birth order >5 were negatively associated.

Conclusion and recommendations: Optimal ANC utilization in countries with high maternal mortality was relatively low. Both individual-level factors and community-level factors were significantly associated with ANC utilization. Policymakers, stakeholders, and health professionals should give special attention and intervene by targeting rural residents, uneducated mothers, economically poor women, and other significant factors this study revealed.

KEYWORDS

antenatal care, women, maternal mortality, low- and middle-income countries, reproductive-age women

Background

Maternal and child mortality remains a substantial public health concern worldwide. However, the risk of these problems is even higher in low- and middle-income countries (1, 2). The United Nations (UN) came up with the Millennium Development Goals (MDGs) to reduce maternal and child mortality in the world community to be achieved by 2015 (3). Despite the country's significant progress in achieving the MDG-5, it has been limited and uneven (4, 5). How the goals were designed, the lack of stakeholder commitment and interest, scarce resources, and lack of accountability were some of the factors for the slow and unequal progress (6, 7).

Complications during pregnancy and childbirth are the leading causes of maternal and child deaths and disabilities (8). The World Health Organization (WHO) recommended antenatal care (ANC) visits as a key strategy to endorse pregnant women's health (9, 10). The organization previously recommended a minimum of four ANC visits throughout the pregnancy; however, it revised its recommended minimum number of ANC visits from four to eight contacts in 2016 to have a safe pregnancy and healthy baby (11). Timely and frequent ANC promotes existing disease treatments, vaccination, malaria prophylaxis, iron supplementation, nutrition counseling, HIV counseling and testing, and urinary tract infection treatment (12–14).

The lowest levels of antenatal care are witnessed in sub-Saharan Africa and South Asia. Individual-level and community-level factors were consistently reported as the most important influences for ANC utilization. In recent studies conducted in low- and middle-income countries, women's education, residence, wealth index, husband's education, mass media, marital status, women's autonomy, husband support, and healthcare accessibility were the commonly reported determinants (15–20). In addition, it is been criticized that the MDG targets were not designed based on enough evidence of feasibility in low-income countries (21, 22). Moreover, limitations in the MDG development process, structure, content, implementation, and enforcement were one of the key obstacles (4, 23–25).

Numerous studies focusing on determinants of antenatal care use in low- and middle-income countries have been conducted and identified important factors. However, a minimum of four ANC visits (ANC4+) utilization in countries with high maternal mortality was not addressed, and getting reliable data on the implementation of MDG and interpretation of progress reports were frequently reported challenges. Identifying gaps in ANC4+ use specifically in these countries is important for stakeholders including policy planners and program managers to increase the utilization of services that decreases maternal–child mortality. In addition, giving a panoramic view of the problem and detecting possible determinates in high maternal mortality countries could help to implement SDG3. Therefore, the objective of our study was to assess the prevalence of ANC4+ visits among women aged 15–49 years and the potential factors associated with it in countries with high maternal mortality. Our study will provide evidence-based recommendations to improve ANC utilization in those reproductive-age women on a large scale.

Materials and methods

Study design and setting

The Demography and Health Surveys employed a cross-sectional study design to collect the data. In this study, we only included countries with high maternal mortality and have publically available DHS data (26).

Data source

This study is a secondary data analysis using the DHS data conducted in 27 countries. The DHS is a nationally representative survey that is conducted in low- and middle-income countries globally. We used individual record (IR) files to extract the study participants of this study. We weighted the sample using the individual weight of women (v005) to produce the proper representation. Hence, sample weights were generated by dividing (v005) by 1,000,000, and the total weighted sample size from the pooled data was 209,538 (Table 1).

Population

Women aged 15–49 years with a birth in the last 5 years receiving antenatal care from a skilled provider for the most recent birth were the study population. Sample weight was used to correct for over- and under-sampling and generalizability of the findings.

Abbreviations: AOR, adjusted odds ratio; ANC, antenatal care; DHS, Demographic and Health Surveys; ICC, intracluster correlation coefficient; IR, individual record; MDG, Millennium Development goal; MOR, median odds ratio; PCV, a proportional change in variance; UN, United Nations; WHO, World Health Organization.

TABLE 1 Maternal mortality, category, and year of the survey by the country.

Country	Year of DHS survey	Maternal mortality/ 100,000	Category
Afghanistan	2018/19	638	Very high
Benin	2017/18	397	High
Burkina Faso	2010	320	High
Burundi	2016/17	548	Very high
Cameroon	2018	529	Very high
Chad	2014/15	1,140	Extremely high
Congo	2011/12	378	High
Côte d'Ivoire	2011/12	617	Very high
Democratic Republic of the Congo	2013/14	473	High
Eswatini	2006/7	437	High
Ethiopia	2016	401	High
Gambia	2019/20	597	Very high
Ghana	2014	308	High
Guinea	2018	576	Very high
Haiti	2017/18	480	High
Kenya	2014	342	High
Lesotho	2014	544	Very high
Liberia	2019/20	661	Very high
Madagascar	2021	335	High
Malawi	2015/16	349	High
Mali	2018	562	Very high
Mauritania	2019/21	766	Very high
Sierra Leone	2019	1,120	Extremely high
Tanzania	2015/16	524	Very high
Togo	2013/14	396	High
Uganda	2016	375	High
Zimbabwe	2015	458	High

High, 300–499; Very high, 500–999; Extremely high, >1,000.

Definition of variables

Outcome variable

Antenatal care visit was the outcome variable for this study. We dichotomized the ANC visits as inadequate and adequate according to the WHO classification (11). Inadequate ANC is <4 visits, whereas optimal if women had four and more visits.

Independent variables

Potential explanatory variables associated with completing optimal ANC visits were considered on two levels. Variables such as mother's age, maternal educational status, parity, marital status, sex of the household head, birth order, and wealth index were used at the individual level, whereas residence, community-level education, community-level poverty, and community-level media exposure were used as community-level variables.

Operational definitions

Community-level media usage is the proportion of women in the community who use radio, TV, and newsletter, and it was categorized as low community-level media usage and high community-level media usage. "Low" refers to communities in which <50% of respondents had media access, while "high" indicates communities in which ≥50% of respondents had media access.

Community-level women's education refers to the proportion of women in the community who have formal education. It was categorized as low if communities in which <50% of respondents had formal education and high if ≥50% of respondents had attended formal education.

Community-level poverty refers to the proportion of women in the community who had low-wealth quintiles. It was categorized as low if the proportion of low-wealth quintile households was <50% and high if the proportion was ≥50%.

Statistical analyses

STATA version 14.2 was used to clean, recode, and analyze the data. A multilevel binary logistic regression model was fitted to identify significantly associated factors. Both community- and individual-level variables with a p-value of ≤0.2 in the bi-variable analysis were included in the multivariable model. Adjusted OR (AOR) with 95% CI and $p < 0.05$ were applied to determine significantly associated factors.

Model building and parameter estimation

Four models were applied, comprising the null model (model 0) containing no variables, which is used to check the variability of ANC visits in the community and provide evidence to assess random effect using the interclass correlation coefficient (ICC). Model I was adjusted for individual-level variables, Model II with community-level factors, and Model III with variables from both individual- and community-level variables were fitted with the outcome variable.

The fixed effect is a measure of association that estimates the association between independent variables and ANC and is stated as AOR with a 95% confidence interval. The Intra-class Correlation Coefficient (ICC), Median Odds Ratio (MOR), and proportional change in variance (PCV) were computed to assess the clustering effect/variability.

Results

Socio-demographic characteristics of respondents

In this study, 209,538 women in 27 countries with high maternal mortality were included. Of the total, about 45.97% were aged 25–34 years and 40.77% had no formal education. The majority of study

participants (86.89%) were married; however, more than a quarter (27.28%) of pregnancies were unwanted. More than half (64.20%) of the participants had media exposure and 15.11% of women had terminated their pregnancies. In our study, around 42.06% of mothers were poor and most of them (69.82%) resides in rural areas (Table 2).

TABLE 2 Socio-demographic characteristics of respondents in high maternal mortality countries.

Variables	Categories	Unweighted frequency (%)	Weighted frequency (%)
Age of mothers	15–24	63,308 (30.03)	62,993 (30.06)
	25–34	96,015 (45.54)	96,331 (45.97)
	>35	51,503 (24.43)	50,214 (23.96)
Mothers educational level	No education	89,596 (42.50)	85,420 (40.77)
	Primary education	70,029 (33.22)	70,297 (33.55)
	Secondary and above	51,201 (24.29)	53,821 (25.69)
Mothers marital status	Not in union	27,409 (13.00)	27,473 (13.11)
	Married	183,417 (87.00)	182,064 (86.89)
Wealth index	Poor	95,412 (45.26)	88,141 (42.06)
	Middle	41,477 (19.67)	41,855 (19.97)
	Rich	73,937 (35.07)	79,542 (37.96)
Media access	No	79,464 (37.77)	74,853 (35.80)
	Yes	130,914 (62.23)	134,255 (64.20)
Mothers occupation	Not working	80,897 (39.89)	79,716 (39.52)
	Working	121,882 (60.11)	121,971 (60.48)
Birth order	1	42,807 (20.30)	43,497 (20.76)
	2–5	120,777 (57.29)	120,555 (57.53)
	>6	47,242 (22.41)	45,485 (21.71)
Ever had a terminated pregnancy	No	172,949 (85.19)	171,420 (84.89)
	Yes	30,067 (14.81)	30,515 (15.11)
Pregnancy	Wanted	149,087 (73.47)	146,796 (72.72)
	Unwanted	149,087 (26.53)	55,066 (27.28)
Sex of household head	Male	167,569 (79.48)	167,160 (79.78)
	Female	43,257 (20.52)	42,378 (20.22)
Residence	Urban	60,959 (28.91)	63,243 (30.18)
	Rural	149,867 (71.09)	146,294 (69.82)
Community-level women education	Low	106,091 (50.32)	102,603 (48.97)
	High	104,735 (49.68)	106,935 (51.03)
Community-level poverty	Low	105,446 (50.02)	108,432 (51.75)
	High	105,380 (49.98)	101,106 (48.25)
Community-level media usage	Low	105,444 (50.01)	101,379 (48.38)
	High	105,382 (49.99)	108,159 (51.62)

The pooled prevalence of ANC4+ visits in countries with high maternal mortality

The pooled prevalence of adequate ANC visits in countries with high maternal mortality was found at 55.66% (95% CI: 47.48–63.85). Ghana (86.05%) had the highest ANC4+ visit and Liberia (85.07%) was in second place. Afghanistan was the country with the least ANC4+ visits, which was 16.19% (Figure 1).

Multilevel logistic regression analysis of adequate ANC visits

In the multilevel analysis, mothers aged 25–34 years, mothers aged 35–49 years, maternal primary, and secondary education and above, working mothers, married, had media access, middle and rich, wanted pregnancy, had terminated pregnancy, female household head, and high community education were significantly associated variables with increased ANC visits while being rural residents and birth orders 2–5 and >5 were associated with low ANC visits (Table 3).

Discussion

Maternal mortality is a major public health problem, particularly in low- and middle-income countries. Early detection and intervention of complications that could happen during pregnancy have a paramount advantage and ANC visit is among those early opportunities. Optimal antenatal care is a key strategy to reduce maternal and child mortality as stated by the WHO and it could be influenced by many factors. Our study revealed a parallel relationship between women's age and ANC4+ contacts, as women's age increases, the odds of ANC4+ visits also increased. Those mothers aged 25–34 years and mothers aged 35–49 years were more likely to have adequate ANC visits compared to mothers aged 15–24 years. This finding is in agreement with previous studies conducted elsewhere (27–29). This could be because older women had more experience and better knowledge because of previous exposure to healthcare providers (30, 31).

In countries with high maternal mortality, the educational status of mothers had a similar directional relationship with ANC4+ visits. Generally, education enables women to obtain a better knowledge of the risk of pregnancy to themselves and their children. Therefore, educated mothers could have increased healthcare-seeking behavior to mitigate this risk and lead to adequate ANC usage (32–35). It has also been reported that education increased women's media penetration of the importance of ANC visits and increased the knowledge of optimal ANC usage importance (36, 37).

Occupation has been linked with ANC4+ visits (38). In our study, working mothers were more likely to have ANC4+ visits compared to their counterparts (39–41). This could be because working mother had their income and might alleviate transportation cost problems. In addition, women who generate an income might be less dependent on their husbands/partners and have better autonomy to utilize ANC

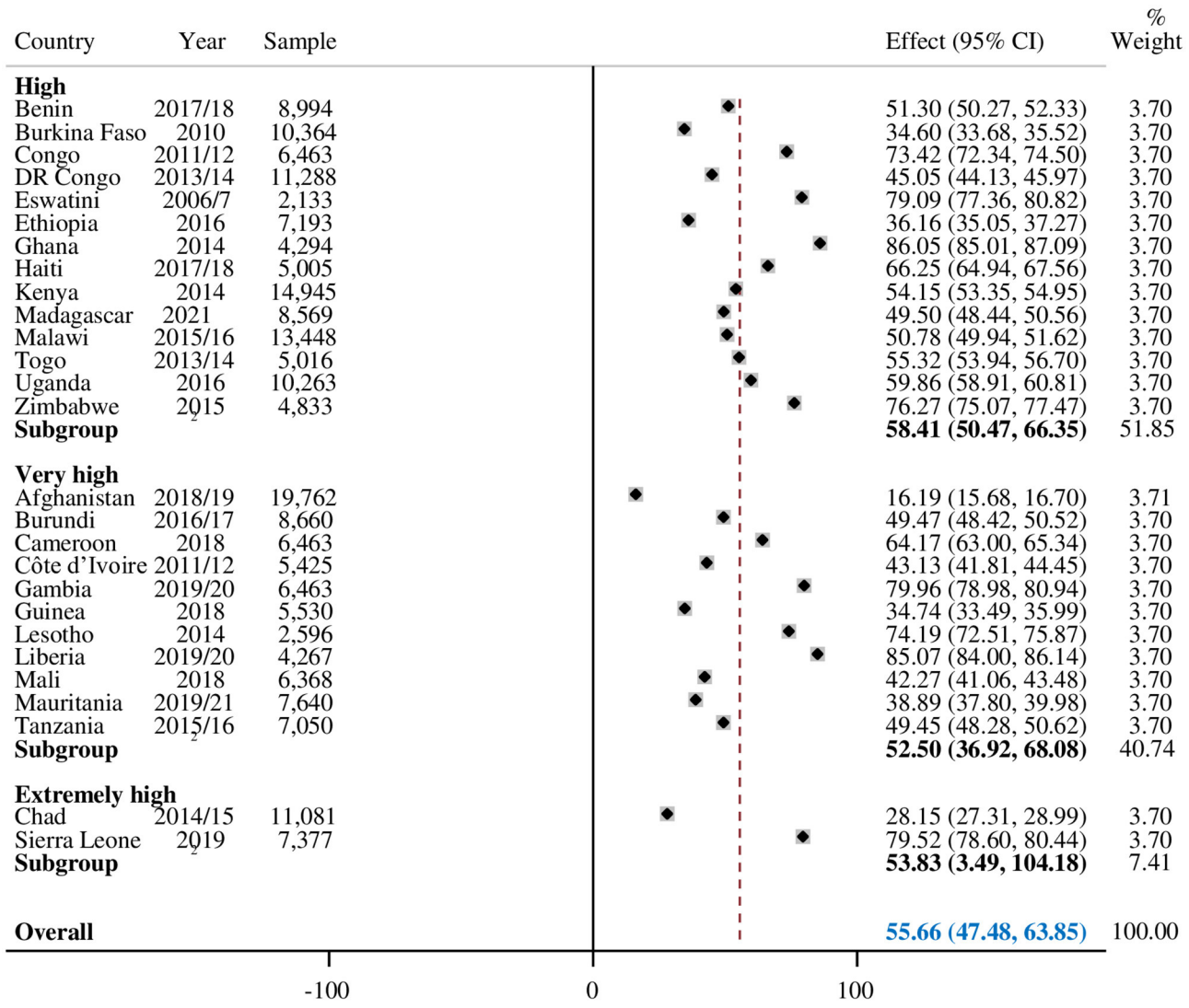

FIGURE 1
The pooled prevalence of optimal ANC in countries with high maternal mortality.

frequently. However, husband/partner cooperation could increase self-esteem, reduce anxiety, and encourage the women to utilize optimal ANC visits (42–44). Husband involvement in ANC follow-up has a crucial role in pregnancy outcomes and is highly recommended by the WHO (45).

Media have been the easiest and quickest to disseminate information related to maternal health which could influence the utilization of ANC frequently. We found that women who had media exposure experienced ANC4+ compared to their counterparts (46, 47). In addition, the wealth index found a significant determinant for women to utilize adequate ANC. In our findings, the household of middle-income and the richest household were more likely to have ANC4+ visits compared to the poorest. Several previous studies were in agreement with this finding (48, 49). Although ANC services are provided for free in low- and middle-income countries, pregnant women who had financial problems may find it difficult to cover laboratory expenses and reach healthcare facilities. This could lead to delaying and inadequate ANC visit, and the impact could be high for those who live far from health institutions as the transportation cost is high.

Pregnancy wantedness has been an important determinant to utilize adequate ANC (50–52). Unwanted pregnancy could be associated with inadequate ANC usage because women might have denial and become careless about the child and their health. On the contrary, women who were pregnant because they want could have better psychosocial support from a partner, family member, relative, or friend who could lend support to the woman if any problem would arise. The introduction of life-saving modern obstetrics is difficult if the psychosocial needs of the women in these poor countries are not being taken care of. This study also revealed that women who had a history of terminated pregnancy were more likely to attend optimal ANC visits. This could be because that mothers who already experienced pregnancy termination for different reasons would be more alert to avoid such problems again and could have optimal ANC. It has been reported that women who assume that pregnancy is a risky event were more likely to attend ANC4+ visits (53).

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TABLE 3 Multivariable multilevel logistic regression analysis results of both individual-level and community-level factors associated with ANC visits in high maternal mortality countries.

Variables	Categories	Null model	Model I AOR [95% CI]	Model II AOR [95% CI]	Model III AOR [95% CI]
Age of mothers	15–24		1.00	————	1.00
	25–34		1.26 (1.22–1.30)***	————	1.24 (1.21–1.28)***
	35–49		1.55 (1.49–1.61)***	————	1.52 (1.47–1.57)***
Mothers educational level	No education		1.00	————	1.00
	Primary education		1.79 (1.75–1.83)***	————	1.79 (1.75–1.83)***
	Secondary and above		3.21 (3.12–3.30)***	————	3.02 (2.94–3.10)***
Mothers occupation	Not working		1.00	————	1.00
	Working		1.39 (1.36–1.42)***	————	1.41 (1.38–1.44)***
Mothers marital status	Not in union		1.00	————	1.00
	Married		1.07 (1.03–1.10)***	————	1.09 (1.06–1.13)***
Birth order	1		1.00	————	1.00
	2–5		0.76 (0.74–0.79)***	————	0.77 (0.74–0.79)***
	>5		0.55 (0.53–0.58)***	————	0.56 (0.55–0.60)***
Media access	No		1.00	————	1.00
	Yes		1.34 (1.31–1.38)***	————	1.31 (1.28–1.33)***
Wealth index	Poor		1.00	————	1.00
	Middle		1.09 (1.06–1.12)***	————	1.04 (1.02–1.07)***
	Rich		1.34 (1.30–1.37)***	————	1.08 (1.05–1.12)***
Pregnancy	Wanted		1.00	————	1.00
	Unwanted		0.93 (0.91–0.95)***	————	0.93 (0.91–0.95)****
Had terminated pregnancy	No		1.00	————	1.00
	Yes		1.17 (1.14–1.20)***	————	1.15 (1.12–1.18)***
Sex of household head	Male		1.00	————	1.00
	Female		1.21 (1.18–1.25)***	————	1.20 (1.17–1.23)***
Community-level variables					
Residence	Urban		————	1.00	1.00
	Rural		————	0.42 (0.41–0.43)***	0.62 (0.61–0.64)***
Com. women's education	Low		————	1.00	1.00
	High		————	1.29 (1.21–1.37)***	1.08 (1.01–1.57)***
Community poverty	Low		————	1.00	1.00
	High		————	1.02 (0.95–1.09)	1.00 (0.94–1.07)
Com. media usage	Low		————	1.00	1.00
	High		————	1.00 (0.93–1.07)	0.99 (0.87–1.06)
Random effect					
	Variance	0.60	0.44	0.50	0.33
	ICC	0.15	0.12	0.13	0.09
	MOR	2.01	1.71	1.83	1.48
	PCV	Reff	26.60	16.60	45.00
Model comparison					
	Log likelihood ratio	−100,585	−92,108	−97,815	−91,665
	Deviance	201,170	184,216	195,630	183,330

***P-value < 0.001.

ICC, intracluster correlation coefficient; MOR, median odds ratio; PCV, proportional change in variance; AOR, adjusted odds ratio; CI, confidence interval; VIF, variance inflation factor; Com. Media, community media usage; Com. women's education, community women's education status.

Birth orders were found significantly associated with ANC4+ utilization. Women who had birth orders 2–5 and >5 were associated with low ANC visits compared with single birth orders. Our finding is also supported by previous studies in Ethiopia (34, 35). This might be due to increased confidence from a previous pregnancy and childbirth experience, and constraints of time and resources among women who had multiple birth orders (54). This study also revealed that place of residence was a significant factor for ANC4+ utilization. The odds of ANC4+ utilization were low among women of rural residents as compared to urban residents. This finding is in line with previous studies conducted in Nigeria (55, 56) and Ethiopia (34, 57, 58). The potential justifications for this discrepancy could be because of inequalities in healthcare service accessibility, infrastructure, and quality in service delivery in the rural and urban setups.

The strength of this study is that it used a large sample size and had adequate power to detect the true effect of the independent variables. It was based on an appropriate statistical method (multilevel analysis) to address the data's hierarchical nature. As a limitation, since the study used cross-sectional data, a causal relationship cannot be established. In addition, because it was based on the information contained in the dataset, potential variables including healthcare access, insurance, and quality healthcare are missed in the analysis.

Conclusion

With high disparity among countries, ANC4+ utilization in countries with high mortality was low. Both individual-level factors and community-level factors were significantly associated with ANC4+ utilization. Therefore, this study revealed that policymakers, stakeholders, and health professionals should give special attention and intervene by targeting rural residents, uneducated mothers, economically poor women, and other significant factors. However, these recommendations should be considered for country-specific contextual factors, considering the different cultural orientations and varied health systems.

Data availability statement

Permission to access the data in this study was obtained from the measure DHS program via online request. The website and the data used were publicly available with no personal identifier.

Ethics statement

The studies involving human participants were reviewed and approved by UOG IRB. The patients/participants provided their written informed consent to participate in this study.

Author contributions

DC: conceptualization. DC, DGB, and AZA: study design. DC, DGB, TAF, KS, MHA, SA, YYS, DMG, MD, and AZA: execution, acquisition of the data, analysis, interpretation, writing, reviewing, and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Maternal and fetal outcomes of pregnant women with bacterial vaginosis

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Background: Bacterial vaginosis (BV) is a common infection in women of reproductive age group because of vaginal dysbiosis. The impact of BV during pregnancy is still not well defined. The objective of this study is to assess the maternal-fetal outcome in women with BV.

Materials and Methods: A prospective cohort study over one-year duration was conducted from December, 2014 until December, 2015, involving 237 women who presented with abnormal vaginal discharge, preterm labour or preterm prelabour rupture of membrane between 22- and 34-weeks period of gestation. Vaginal swabs were sent for culture and sensitivity, BV® Blue testing and PCR for Gardnerella vaginalis (GV).

Results: BV was diagnosed in 24/237 (10.1%) cases. The median gestational age was 31.6 weeks. GV was isolated from 16 out of 24 (66.7%) in the BV positive group. There was a significantly higher preterm birth rate, below 34 weeks (22.7% vs. 6.2%, $p = 0.019$) in women with BV. There was no statistically significant difference in maternal outcome such as clinical chorioamnionitis or endometritis. However, placental pathology revealed more than half (55.6%) of women with BV had histologic chorioamnionitis. Neonatal morbidity was significantly higher with exposure to BV, with a lower median birth weight, higher rate of neonatal intensive care unit admission (41.7% vs. 19.0%, $p = 0.010$), increased intubation for respiratory support (29.2% vs. 7.6%, $p = 0.004$) and respiratory distress syndrome (33.3% vs. 9.0%, $p = 0.002$).

Conclusion: More research is needed to formulate guidelines for prevention, early detection and treatment of BV during pregnancy to reduce intrauterine inflammation and the associated adverse fetal outcomes.

KEYWORDS

preterm birth, preterm labour, BV® blue, neonatal intensive care unit, Gardnerella vaginalis, vaginal discharge, rupture of membrane, histologic chorioamnionitis

Introduction

Bacterial vaginosis (BV) is an imbalance of normal genital tract microbiota, where depletion of hydrogen-peroxide producing lactobacilli is replaced by *Gardnerella vaginalis* (GV), *Mobiluncus, Bacteroides spp*, and *Mycoplasma hominis* (1, 2). Gardner and Duke reported a syndrome called non-specific vaginitis in the 1950s, which was re-named bacterial vaginosis. Without using anaerobic culture techniques, the microaerophilic microorganism Haemophilus (*Corynebacterium, now renamed Gardnerella*) vaginalis was said to be the sole etiology of BV (3). With today's improved culture and diagnostic technique, BV consists mainly of anaerobic

bacteria in the mixed flora. These obligate anaerobic bacteria appear side by side with *Gardnerella vaginalis and Mycoplasma hominis* (3).

BV is a common disorder in women of childbearing age. Women may have classical symptoms of grey, homogenous malodorous discharge but up to 80% of them were asymptomatic (4). It affects 6.4 to 16% of pregnant women (5–9) and has been linked to several obstetrics complications including preterm birth, preterm premature rupture of membrane, intra-amniotic infection, postpartum endometritis, as well as neonatal complications i.e., respiratory distress syndrome (RDS) and neonatal intensive care unit (NICU) admission (10–12). Even so, reports of associated complications are still variable and not consistent, depending on the origin of the studies.

The diagnosis of BV remains difficult and controversial. Amsel's criteria include the homogenous greyish white appearance of vaginal discharge, presence of clue cells on a wet mount, vaginal pH of more than 4.5 and a positive whiff test. The diagnosis of BV requires 3 out of 4 criteria (13). On the other hand, Nugent's scoring system (0 to 10) was described as a weighted combination of the following morphotypes: *Lactobacilli sp*, *Gardnerella vaginalis* or *Bacteroides sp*, and curved gram variable rods (14). In this method, a score of 0–3 represents normal flora, 4–6 intermediate, and 7–10 as BV. The sensitivity and specificity of Amsel criteria were 51.2–88.3% and 92%–98% respectively (7, 15); whereas Nugent's score was 46%–89% and 83%–95% respectively (15, 16). However, both methods required trained personnel for slide preparation and result interpretation which could be a major drawback.

Recently, a bedside rapid test to diagnose BV has gained much popularity. The BV® Blue test is a chromogenic diagnostic test based on the presence of elevated sialidase enzyme in vaginal fluid samples that were produced by organisms causing BV (17). The sensitivity and specificity reported were 88%–100% and 95–98.3% as compared to Nugent's method (17–19). Whereas, the positive predictive value (PPV) and negative predictive value (NPV) were 91.7–94.4% and 97.8%–100% (17, 18). Thus BV® Blue test was chosen to diagnose BV in this study.

With the advancement in cultivation-independent methods like Polymerase Chain Reaction (PCR), the presence of newly diagnosed vaginal species such as *Fannyhessea vaginae* (formerly known as *Atopobium vaginae*) and three bacterial species in the *Clostridiales* order that were highly specific for BV were revealed (20). A study using semi-quantitative multiplex PCR assay by Kusters et al. showed the presence of GV in 96% of women with a Nugent score of 7–10 and GV only present in 27% if Nugent score was 1–3 (21). By using this technique, the BV-PCR displayed a sensitivity of 92% and specificity of 96% with a PPV and NPV of 94% and 95% respectively (21). Another study by Rumyantseva et al. evaluated the diagnostic value of Nugent score, wet mount microscopy and PCR test and showed that agreement among the three methods was 73.5% (72 out of 98 samples) (22). PCR quantifies Deoxyribonucleic Acid (DNA) rather than the viable organism. This is a potential advantage as it can detect the organism in archived genital tract samples that were collected under a condition that were not optimized for organism viability. PCR is also highly sensitive and able to pick up a very low number of bacteria.

Isolation of GV in BV may be of clinical and therapeutic importance. A high bacterial load of GV was found to be associated with preterm birth, with a hazard ratio of 3.9 (23). Molecularly, GV was reported to be the major component that was responsible for 90% of bacterial biofilm on vaginal epithelium (24). GV biofilms also exhibited higher tolerance to hydrogen peroxide, initiate BV establishment, facilitate the growth of other BV-associated anaerobes and resist repeated intravaginal antiseptic treatment (25, 26).

In Malaysia, there has been a paucity of data concerning maternal and fetal outcome in women with BV. The objectives of this study were to assess the feto-maternal outcome in women diagnosed to have BV. The prevalence of GV in BV-positive women was assessed as well.

Materials and methods

Study design

Pregnant women who presented with abnormal vaginal discharge, preterm pre-labour rupture of membrane (PPROM) or preterm labour, gestational age from 22 weeks to 34 weeks, singleton pregnancy, and those who consented to the study were recruited. Abnormal vaginal discharge was defined as a change in colour (such as grey, green or yellow, or blood-stained), copious amount, or odour, associated with itchiness or soreness. Preterm labour was defined as having regular contractions of at least 2 in 10 min with cervical effacement and cervical os dilatation. Pregnant women with the following criteria were excluded: obstetric complications that can be confounding factors for preterm delivery such as pre-existing medical disorders e.g., diabetes, hypertension, cardiac and renal disease, and all complicated pregnancies (antepartum hemorrhage, fetal anomaly, multiple gestation, intrauterine growth restriction, or polyhydramnios. Oligohydramnios caused by IUGR or fetal anomalies were excluded. However, oligohydramnios following PPROM during enrolment was not our exclusion criteria). Women who had cervical incompetence, uterine or cervical anomaly, fetal death, and history of recent douching, or sexual intercourse pre-testing, as well as recent use of systemic or vaginal antimicrobial therapy either as suppository drugs or spray within the preceding 72 h were excluded from the study.

Procedure

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Medical Research and Ethics Committee of Universiti Kebangsaan Malaysia (FF-2015-037). All eligible pregnant women were informed about the study and they were provided with a patient information leaflet. Written consent was obtained. A detailed history, physical examination, and sterile speculum examination were performed either in the antenatal clinic or patient admission centre of the Department of Obstetrics and Gynaecology, Universiti Kebangsaan Malaysia Medical Centre. All the details were recorded on a proforma.

Vaginal fluid was collected during speculum examination in the following manner. Women were positioned in the dorsal position. A Cusco speculum was inserted without any lubricant. Characteristics of the vaginal discharge were noted. Three samples were then obtained from the posterior vaginal fornix using sterile cotton-tipped swabs. The first swab was sent for culture and sensitivity to look for any organism that might cause the vaginal discharge such as *Candida spp* or *Group B Streptococcus*. The second sample was obtained for BV® Blue testing to diagnose BV.

For the BV® Blue test, the swab was immersed into the BV® Blue Testing Vessel that contained a chromogenic substrate of bacterial sialidase at room temperature (24–32 °C). The vessel was left standing for 10 min. The test vessel was checked to ensure it contained only colourless fluid without sediment. Subsequently, one drop of BV® Blue Developer Solution was added into the testing vessel and swirled. Then, the result was read immediately. A positive result was interpreted as a change of colour to blue or green while yellow was a negative result. If the result was not blue/green or yellow, then the test was repeated. For those with BV® Blue tested positive, the third swab would be sent to the laboratory for detection of GV using the PCR method. For those who tested negative, the third swab for GV was discarded. To reduce interpersonal data interpretation errors, these tests were performed by a single operator.

PCR setup

GV was selected in this study as it was thought to be the main contributing bacteria in bacterial vaginosis. Isolation of its DNA from the vaginal swab was performed using InnuPREP DNA Mini Kit based on the extraction protocol as advised by the manufacturer. The extraction procedure involved a lysing step, followed by binding of genomic DNA on a Spin Filter surface, washing of the bound DNA, and eluting of the DNA. The presence of GV was established by qualitative PCR. The amplifications were carried out in an automated Gene Amp PCR System 9,700 (Perkin-Elmer Cetus, CT, USA) using MyTaq™ HS Mix as specified by the manufacturer. Forward and reverse primers were used (GVF: TTCGATTCTGGCTCAGG and GVR: CCATCCCAAAAGGGTTAGGC) at the concentration of 0.25 μM. Reactions were performed in a final volume of 25 µl. PCR conditions consisted of a heat-activated Taq polymerase of 95 °C for 60 s followed by 35 cycles of amplification. Each amplification cycle consisted of a denaturation step at 95 °C for 15 s, an annealing step at 55 °C for 15 s and finally extension step at 72 °C for 10 s. The PCR product is detected by 1.2% (w/v) agarose gel electrophoresis with 1X Tris/Borate/EDTA (TBE) buffer. The GV (ATCC 14108) was used as a positive control along with a "No Template Control" and were amplified together with the samples.

All patients with a positive BV® blue test were treated with Dequalinium Chloride vaginal pessary (Fluomizin® Medinova, DKSH) 1 tablet daily for 6 days. Other than Dequalinium chloride vaginal pessary, patients with preterm labour or PPROM were also managed per standard hospital protocol. All patients were followed up till delivery and post-partum. The outcomes of pregnancy were recorded for both the mother and baby. Upon delivery, a small portion of the placenta tissue was sent for histopathology examination for evidence of chorioamnionitis. The neonatal outcomes such as the need for intubation, antibiotic administration, days of admission to NICU, presence of respiratory distress syndrome, baby's cord pH, Apgar score, and neonatal death were recorded. Patients were called *via* phone at six weeks postpartum by the investigator to enquire about any postpartum complications such as postpartum endometritis or wound breakdown. Questions included a history of fever and persistent lochia which was excessive, purulent, or malodorous to suggest endometritis or history of discharge or pus from the wound, redness, and pain, suggestive of wound breakdown. If they have such a complaint, they were asked to present to the patient admission centre immediately.

Data analysis

SPSS (Statistical Package for Social Science) version 23 was used for data analysis. Participants' profiles were presented descriptively in terms of frequency and percentage, mean and standard deviation (for normally distributed data), or median and interquartile range (for non-normally distributed data). Non-parametric statistical tests (Mann-Whitney test) were used for variables such as maternal age, monthly income, gestational age during recruitment, gestational age during delivery, the interval between recruitment and delivery (**Tables 1**,**2**) as well as birth weight and cord pH (**Table 3**). The chi square test was used to compare two categorical data in **Tables 1**–**3**. A significant level was set at $p < 0.05$.

Results

A total of 251 pregnant women were eligible and consented to the study. However, 14 were excluded as eight of them were lost to follow-up after being discharged from the ward and the other four had their deliveries at other hospitals, and the delivery information was unable to be traced. Two women refused to give consent for placental HPE to be conducted in this study. Thus, we had a response rate of 94.4% i.e., 237 pregnant women were available for final data analysis. The demographic data were shown in **Table 1**. The median age for the study sample was 30.0 years (27.0, 33.0). It was comparable in both the positive group (BV positive) and the control group (BV negative). Almost all of the pregnant women were married (98.3%) and the ethnic distribution was similar to the ethnic distribution in the country. The majority were Malay (67.9%), followed by Chinese (23.2%), Indian (4.2%), and others (4.6%). More than half of the pregnant women were multiparous (58.4%) with a median monthly income of 3,500 Malaysian Ringgit (approximately 750 US dollars). The demographic data were similar between the positive and the control group (**Table 1**).

Further analysis of patients' clinical characteristics showed that the majority of them presented with abnormal vaginal discharge (73.0%), followed by preterm labour (19.4%) and least commonly, PPROM (7.6%). This was not different statistically between the positive and control group ($p = 0.772$). The median gestational age at recruitment was 31.6 weeks and it was comparable in both the

TABLE 1 Patient socio-demographic characteristics.

	All ($n = 237$)	BV positive ($n = 24$)	BV negative ($n = 213$)	p-value
Maternal age (years)	30.0 (27.0,33.0)	29.0 (26.0, 32.0)	30.0 (27.0, 33.0)	$p = 0.321$
Marital status, *n* (%)				
• Married	233 (98.3)	24 (100.0)	209 (98.1)	$p = 0.498$
• Single	3 (1.7)	0 (0.0)	4 (1.9)	
Ethnicity, *n* (%)				
• Malay	161 (67.9)	16 (66.7)	145 (68.1)	$p = 0.670$
• Chinese	55 (23.2)	7 (29.2)	48 (22.5)	
• Indian	10 (4.2)	0 (0.0)	10 (4.7)	
• Others	11 (4.6)	1 (4.2)	10 (4.7)	
Educational level, *n* (%)				
• Primary	8 (3.4)	0 (0.0)	8 (3.8)	$p = 0.409$
• Secondary	104 (43.9)	13 (54.2)	91 (42.7)	
• Tertiary	125 (52.7)	11 (45.8)	114 (53.5)	
Monthly income (RM)	3,500 (3,000, 5,000)	4,000 (2,575, 5,000)	3,500 (3,000, 4,950)	$p = 0.676$
Nulliparous, *n* (%)	101 (42.6)	13 (54.2)	88 (41.3)	$p = 0.227$

Data expressed in median (Quartile) unless specified.

positive and control group (32.1 vs. 31.1, $p = 0.768$). However, patients in the BV positive group had a significantly higher percentage of preterm birth, below 34 weeks gestation (22.7% vs. 6.2%, $p = 0.019$) and lower gestational age upon delivery (37.3 vs. 38.1 weeks, $p = 0.010$) as compared to the negative control group. Thus, the interval between patient recruitment and delivery was also noted to be significantly shorter in the positive group as compared to the control group (4.8 vs. 7.2 weeks, $p = 0.026$). In analysing the three subgroups separately, it is noteworthy that the gestational ages at recruitment were similar, however, gestational age at delivery was significantly lower in the BV positive group, being shortest in the preterm labour group, median 33.8 weeks vs. 37.0 weeks in the BV negative group. This is not statistically significant when looking at each subgroup separately, likely because the sample size is small. Collectively, the BV-positive subgroup also showed a significantly shorter average interval (4.8 weeks) from presentation and recruitment to delivery as opposed to the BV-negative group (7.2 weeks) (Table 2). There was no statistically significant difference in the mode of delivery (vaginal delivery vs. caesarean section) between the two groups ($p = 0.624$). One in two patients with BV positive also had concurrent vaginal infections such as candidiasis and group B streptococcus infection but this was not significantly different from the BV negative group (Table 2).

There was no statistically significant difference in any maternal outcome such as primary postpartum haemorrhage (PPH), endometritis and wound breakdown between the positive and control groups ($p = 0.498$, $p = 0.180$ and $p = 0.061$ respectively). Two patients (one in each group) had perineal wound breakdown after vaginal delivery (Table 3). There was no overt/clinical chorioamnionitis in both groups. However, babies born to mothers with BV had significantly lower median birth weight (2,450 grams vs. 2,950 grams, $p = 0.007$). These babies were also noted to have a lower median cord pH (7.256 vs. 7.330, $p = 0.004$), which was of doubtful clinical relevance as it was still within the normal range. Of note, babies born to mothers with BV had more than double the NICU admission rate (41.7% vs. 19.0%, $p = 0.010$), almost four-fold higher rate of endotracheal intubation (29.2%% vs. 7.6%, $p = 0.004$) and RDS (33.3% vs. 9.0%, $p = 0.002$). There was no perinatal death in the BV positive group as compared to the control group ($n = 5$) (Table 3) The placental HPE showed evidence of acute chorioamnionitis up to 55.6% in the BV positive group. GV was positive in 16 out of 24 BV positive patients.

Discussion

The prevalence of BV in this study was 10.1% (diagnosis by BV® Blue test). The reported prevalence in the literature was widely different based on different populations of study samples, diagnostic tools used, and whether the studies were done in a community setting or academic medical centre (27).

This study was consistent with a cohort study done by Purmar et al. among 1,006 pregnant women between 16 and 28 weeks gestation, in which the prevalence of BV was reported to be 11.5% (by Nugent's criteria) (6). Larsson et al. (8) reported similar findings in their reviews. However, the prevalence of this study was lower than the review by Svare et al. among 3,540 pregnant women at University Hospital Denmark, in which BV was detected in 16% of their subjects (9). Our study was conducted on pregnant women who presented with vaginal discharge, preterm labour and PPROM. We would expect our finding of BV to be higher as compared to others that studied asymptomatic pregnant women, which were considered a low-risk population. Looking at the prevalence of BV among 152 women with preterm labour, Laxmi et al. reported the detection of BV up to 24.3% in their subjects (12). Another study by Thanavuth et al. reported that the prevalence of BV was higher in women with preterm labour as compared to women presented with preterm contraction only (25.8% vs. 14.1%) (28). In our study, the prevalence of BV in patients who presented with preterm birth was 20.9%.

Previous studies had looked into risk factors for antenatal BV. Larsson et al. reported that the prevalence of BV was significantly higher in women who smoke and in the younger age group, but not in those with a history of previous preterm delivery (8). Whereas, Kirakoya et al. identified Herpes Simplex Virus type-2 infection as the only factor associated with an increased risk of BV (5). Pastole et al. concluded that 6 predictors i.e., vaginal pH > 4.5, black race, condom use during pregnancy, antenatal BV earlier in the index pregnancy, absence of sperm on smear, and no history of sexually transmitted disease could be used to predict the risk of antenatal BV. This scoring system had a sensitivity and specificity of 77% (4). In this study, we were unable to demonstrate any significant association between maternal age, marital status, educational level, and parity concerning the risk of BV.

TABLE 2 Patient clinical characteristics.

	All (237)	BV positive (24)	BV negative (213)	*p*-value
Presenting complaint, *n* (%)				
• Abnormal vaginal discharge	173 (73.0)	16 (66.7)	157 (73.7)	$p = 0.742$
• Preterm labour	46 (19.4)	6 (25.0)	40 (18.8)	
• PPROM	18 (7.6)	2 (8.3)	16 (7.5)	
Gestational age at recruitment, weeks	31.6 (28.5, 33.1)	32.1 (27.7, 32.9)	31.1 (28.5,33.1)	$p = 0.768$
• Abnormal vaginal discharge	30.9 (28.1,33.0)	32.2 (30.0,32.9)	30.7 (28.0,33.0)	$p = 0.330$
• Preterm labour	32.1(30.0,33.6)	32.0 (26.3,33.2)	32.1 (30.0,33.6)	$p = 0.493$
• PPROM	32.8 (28.2,33.4)	29.1 (24.9,-)	32.8 (29.2,33.4)	$p = 0.526$
Gestational age at delivery, weeks	38.0 (36.4, 39.1)	37.3 (34.0, 38.3)	38.1 (36.7, 39.3)	$p = 0.010$
• Abnormal vaginal discharge	38.3 (37.4,39.3)	38.0 (36.0, 38.9)	38.4 (37.6,39.6)	$p = 0.077$
• Preterm labour	37.0 (34.0,38.4)	33.8 (32.3, 37.6)	37.0 (34.7, 38.9)	$p = 0.108$
• PPROM	34.8 (33.9,37.0)	34.2 (33.9, -)	35.2 (33.9,37.0)	$p = 0.439$
Interval between recruitment and delivery, weeks	6.9 (4.5,10.0)	4.8 (1.5,8.9)	7.2 (4.7,10.0)	$p = 0.026$
• Abnormal vaginal discharge	7.8 (5.2,10.5)	5.5 (2.9,9.2)	8.0 (5.4,10.7)	$p = 0.097$
• Preterm labour	4.6 (0.6,7.2)	0.6 (0.0, 11.2)	4.9 (2.8,7.0)	$p = 0.369$
• PPROM	3.3 (1.0,6.0)	5.2 (1.3,-)	3.3 (1.0,5.6)	$p = 0.673$
Preterm birth <34 weeks, n(%)	17 (7.9)	5 (22.7)	12 (6.2)	$p = 0.019$
• Abnormal vaginal discharge	2 (0.9)	1 (4.5)	1(0.5)	$p = 0.177$
• Preterm labour	10 (4.7)	3 (13.6)	7 (3.6)	$p = 0.107$
• PPROM	5 (2.3)	1 (4.5)	4 (2.1)	$p = 0.490$
Mode of delivery, *n* (%)				
• Vaginal delivery	177 (74.7)	16 (66.7)	161 (75.6)	$p = 0.624$
• Caesarean Section	60 (25.3)	8 (33.3)	52 (24.4)	
Concurrent infection, *n* (%)	101 (42.6)	12 (50.0)	89 (41.8)	$p = 0.367$

All parameters are expressed in median (interquartile range) unless specified. PPROM, Preterm prelabour rupture of membrane.
[a]Total = 17/215, excluding 22 cases who were recruited after 33 weeks; BV positive, $n = 5/22$; BV negative, $n = 12/193$.

TABLE 3 Maternal-fetal outcome according to bacterial vaginosis status.

	All ($n = 237$)	BV positive ($n = 24$)	BV negative ($n = 213$)	*p*-value
Primary PPH, *n* (%)	4 (1.7)	0 (0.0)	4 (1.9)	$p = 0.498$
Endometritis, *n* (%)	3 (1.3)	1 (4.2)	2 (0.9)	$p = 0.180$
Wound breakdown, *n* (%)	2 (0.8)	1 (4.2)	1 (0.5)	$p = 0.061$
Birth weight (grams)	2,930 (2,510, 3,195)	2,450 (2,150, 2,957)	2,950(2,600, 3,200)	$p = 0.007$
Apgar score ≤7 at 5th minute	13 (5.6)	3 (12.5)	10 (4.8)	$p = 0.117$
Cord pH	7.324 (7.265, 7.367)	7.256 (7.227, 7.343)	7.330 (7.275, 7.369)	$p = 0.004$
NICU admission, *n* (%)	50 (21.4)	10 (41.7)	40 (19.0)	$p = 0.010$
Baby intubated, *n* (%)	23 (9.8)	7 (29.2)	16 (7.6)	$p = 0.004$
RDS, *n* (%)	27 (11.5)	8 (33.3)	19 (9.0)	$p = 0.002$
Perinatal death, *n* (%)	5 (2.1)	0 (0.0)	5 (2.3)	$p = 0.448$

Even though most of the women with BV infection were asymptomatic (4), efforts should be made to identify and diagnose this infection when pregnant women presented to health care providers as it was associated with adverse fetal outcomes. Most of our patients with BV positive presented with abnormal vaginal discharge instead of preterm labour or PPROM. Thus, a simple and inexpensive bedside rapid test to diagnose BV should be made available in all settings where possible, allowing rapid commencement of treatment. We used the BV® Blue test to diagnose BV in this study. The sensitivity and specificity reported were 88%–100% and 95–98.3% as compared to Nugent's method (17–19), and the positive predictive value (PPV) and negative predictive value (NPV) were 91.7–94.4% and 97.8%–100% (17, 18).

In this study, we demonstrated that BV-positive women had a statistically significant higher rate of moderate preterm birth (below 34 weeks gestation), up to almost four-fold, and delivered at an earlier gestational age despite being given treatment. In a sub-analysis of women with preterm labour only, BV-positive women delivered at the median gestational age of about 34.0 weeks as compared to 37 weeks in those who were BV-negative. This was consistent with a meta-analysis by Leitich et al. that included eight studies with 20,232 patients. Bacterial vaginosis was associated with a 2-fold increased risk of preterm delivery with an odds ratio of 2.9 (2). A similar finding was reported by Purwar et al. in which the incidence of preterm labour and PPROM was significantly higher in BV positive women as compared to BV negative women ($p = 0.001$). Our study also showed that in BV positive women presenting with vaginal discharge alone, the average gestational age at delivery was 38 weeks with a shorter average interval to delivery of 5.5 weeks. This was not statistically significant. Larger population sampling from international multicentre trials is needed to confirm this important observation.

The overall preterm delivery rate in this study was as high as 24.2% (gestational age range from 23.9 to 36.9 weeks) with the prevalence of BV at 10.1%. This was contrary to the study by Svare et al. in which the prevalence of BV was 16% in 3,540 women and the preterm delivery rate was only 5.2%. In their review, BV had a statistically significant association with preterm delivery, low birth weight infant and clinical chorioamnionitis (9). On the other hand, Donders et al. found that the presence of BV was associated with a 2.4-fold increased risk of preterm delivery (10). This was consistent with the study by Guaschino et al. in which the presence of BV before 16-week gestation had a 2-fold increased risk of preterm birth (11). In our study, 50% (9 out of 18) of those with BV positive had a preterm birth, whereas only 21% of those with BV negative had a preterm birth.

There was no statistically significant association between adverse maternal outcomes and bacterial vaginosis in this study. The rate of primary PPH between the two groups was not different. The rate of endometritis and wound breakdown were not significantly higher in BV-positive women, consistent with the study by Larsson et al. (8). Conversely, Watts et al. reported that BV was a risk factor for post-caesarean endometritis (29). However, our numbers for adverse maternal outcomes were too small to draw any solid conclusion.

BV was a risk factor for increased neonatal morbidity as demonstrated by previous studies (12, 29). A study by Laxmi et al. reported that admission to NICU, NICU stays of more than 2 days, the need for intermittent positive pressure ventilation and RDS were higher in infants born to women with BV infections (12). However, there was no difference in mean birth weight, Apgar score at 5 min, or risk of neonatal sepsis or perinatal mortality (12). Another study by Subtil et al. showed a significant difference in Apgar score at 5 min but not the risk of NICU admission or perinatal death (30). In our study, we demonstrated that babies born to BV-positive women had a significantly higher rate of admission to NICU, need for intubation, and RDS. The length of stay in the NICU ranged from 2 to 7 days. The placental HPE showed evidence of acute chorioamnionitis in up to 55.6% of the BV positive cases.

A recent Cochrane review by Sangkomhang et al. revealed that antenatal lower genital tract infection screening and treatment reduced the rate of preterm birth significantly and is cost-saving (31). Another Cochrane review of 21 good quality trials by Brocklehurst et al. demonstrated that antibiotic treatment was effective in eradicating BV in pregnancy with a risk ratio of 0.42 (32). A meta-analysis published recently evaluated the clinical cure rates (CCRs) for BV based on randomized controlled trials of different therapies and administration routes. The highest *P*-scores in CCRs were obtained by a combination therapy with probiotic treatment and the application of antibiotics (oral clindamycin and local 5-nitroimidazole) (33). However, a clear-cut decision for the best BV treatment was not possible due to the heterogeneity of outcomes reported in those trials (33). In our study, Fluomizin® was used to treat women with BV. It had been shown that vaginal Fluomizin® tablet was as effective as Clindamycin cream with a cure rate of 81.5% and 78.4% respectively (34). However, treatment was not given to two patients with BV due to imminent deliveries. The antenatal treatment impact on neonatal morbidity is still undefined. In our series, in the absence of therapy, there was a BV positive patient who presented with preterm labour at 32 weeks of gestation, but delivered soon after admission to a baby weighing 2,100 grams with a cord pH of 7.24. The baby required NICU admission, was intubated and was diagnosed to have RDS. The placental HPE confirmed acute chorioamnionitis. Another BV positive patient presented at 34 weeks of gestation and delivered within 5 h of presentation to a baby weighing 2,470 grams. The baby did not require NICU care and was discharged well to the mother without complication, although placental HPE was suggestive of acute chorioamnionitis.

Lastly, the isolation of GV in patients with BV infection had been reported by previous studies. It had been shown that a high GV load was associated with an increased risk of preterm birth and intra uterine growth restriction. Therefore, the role of GV in bacterial biofilm should not be overlooked (23, 35, 36, 37, 38). We managed to isolate GV in two-thirds of our patients with BV using the qualitative PCR technique. This was relatively lower as compared to a study by Spiegel et al. in which GV was isolated in all 25 patients diagnosed to have bacterial vaginosis (39); as well as a review by Aroutcheva et al. in which GV has isolated in 28 (87.5%) women with BV (40). This could be due to the difference in our population, in the assay method used. To date, there is no study comparing the performance of different methods of PCR assays in detecting GV. However, Caliendo et al. (41) in their

study compared the performance of the qualitative and quantitative PCR assays for cytomegalovirus DNA in the plasma, having shown that qualitative assays had lower sensitivity than the quantitative ones.

The strength of our study is that we screened, diagnosed and treated BV early. It is the unit protocol to use Fluomizin rather than the Center of Disease Control recommendation of using Metronidazole 500 mg orally 2 times/day for 7 days OR Metronidazole gel 0.75% one full applicator (5 g) intravaginally, once a day for 5 days OR Clindamycin cream 2% one full applicator (5 g) intravaginally at bedtime for 7 days (42). Using Fluomizin was based on local availability and preference, although not robustly evidence-based. However, the use of a non-antibiotic agent may reduce the development of antimicrobial resistance. This study was not intended to compare treatments, as such future trials are needed to investigate this aspect. Nevertheless, we speculate that early treatment following diagnosis of BV in pregnant women with vaginal discharge, preterm labor or PPROM may have reduced the extent and limited the severity of preterm births, or perhaps adverse outcomes such as perinatal loss or mortality. We also investigated if babies were of lower birth weight when exposed to GV antenatally following our animal model that showed this outcome (38). Further studies are required to confirm this.

There were several limitations in this study. We only included symptomatic women that presented with abnormal vaginal discharge, preterm labour or PPROM. Thus, the prevalence of BV in this study might not represent the entire population. Larger population studies are needed to confirm the attributable risk for preterm birth in pregnant women with BV. We have also focused on GV as the sole aetiology of BV. The selection criteria could not tease out the different risk factors predisposing to BV and how these may affect outcomes separately as the numbers in the preterm labour and PPROM groups separately were small. Although our study showed that BV was associated with preterm births, we did not include information such as cervical length or fibronectin test as well. Future larger studies looking at preterm labour itself are needed to confirm that BV hastens delivery in such circumstances. The need for tocolytic treatment and the use of dexamethasone was individualized, which should have been controlled in future trials to prevent bias in the reported outcomes. More sophisticated bacterial detection and identification, and real-time PCR testing to relate the severity of bacterial load against disease and outcomes may be some considerations to incorporate in future trials.

Conclusion

Our study showed that BV in pregnancy is associated with a significant risk of infants born preterm, with the interval from diagnosis of BV to delivery on average more than 2 weeks shorter than women without BV. Infants born preterm at a lower median birth weight are associated with an increased risk of neonatal morbidities such as RDS requiring NICU admission and respiratory support. There was no significant association with adverse maternal outcomes such as primary PPH and endometritis. More research is needed to study the preventive, diagnostic, and therapeutic approaches in association with a primarily adverse fetal outcomes as a result of BV in pregnancy.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Research and Ethics Committee of Universiti Kebangsaan Malaysia. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JNC, BKN, CFCC, MIN, GCT, KKW and PSL contributed to the study design. JNC was involved in data collection and data entry. JNC and BKN were responsible for data analysis and final writing of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case report: Emergency presentation of Meckel's diverticulum in the 3rd trimester of pregnancy

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Background: Symptomatic Meckel's diverticulum (MD) is easily neglected in the acute abdomen during pregnancy. MD is the most common congenitally anomalous development of the intestines, with an incidence of 2% in the general population, although it is not easily diagnosed because of variable clinical features. Especially when complicated with pregnancy, doctors can easily overlook this disease, which directly threatens maternal and foetal life.
Case Presentation: We report the case of a 25-year-old at 32 + 2 weeks of gestation complicated with MD volvulus who presented with progressive abdominal pain and finally peritonitis. She underwent exploratory laparotomy and small-bowel resection. The mother and the baby successfully recovered.
Conclusions: MD-complicated pregnancy is not easily diagnosed. Once highly suspiciously diagnosed, especially with peritonitis, surgery should be arranged, which helps preserve maternal and foetal life.

KEYWORDS
meckel's diverticulum, acute abdomen, pregnancy, emergency, obstetric (third trimester)

Introduction

MD is the most common congenital anomaly of the gastrointestinal tract, caused by incomplete obliteration of the omphalomesenteric duct in the developing embryo, which has an incidence of 2% (1, 2). Patients with MD are usually asymptomatic, while 3.7%–6.4% present various symptoms, such as small-bowel obstruction, peritonitis, appendicitis, cholecystitis, renal colic disease, or peptic ulcer disease (3, 4). MD is easily misdiagnosed because the clinical features vary between individuals. In particular, MD complicates late pregnancy, and the diagnosis can be delayed, leading to high mortality of the mother and foetus.

Here, we report a young woman at 32 + 2 weeks of gestation complicated with MD volvulus who presented with progressive abdominal pain and finally peritonitis. Meckel's diverticulum is the third trimester of pregnancy is rare. We summarized five such cases that we found in the existing literature in **Table 1**.

Case presentation

A 25-year-old at 32 + 2 weeks gestation arrived at the hospital because of abdominal pain with a recent ingestion of spicy food. Approximately 4 h later, she felt abdominal colic pain, which improved spontaneously or by changing position, with vomiting 5 times. Without diarrhoea, she defecated normal soft stool twice. She had no fever. The pain was not relieved after she received the phloroglucinol at a dose of 40 mg iv in the outpatient department. Then, she was transferred to the inpatient department for treatment at 17:00.

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TABLE 1 Cases of Meckel's diverticulum in the third trimester of pregnancy.

Age (years)	Gestational age (weeks)	Symptoms	Peritonitis	Imaging	Treatment	Result	Apgar scores (1,5 min)
34	34	Abdominal pain	+	Abdominal x-ray	Surgery	Mother and baby recovered	6,9 (5)
14	32	Abdominal pain, distension	+	CT	Surgery, the patient was discharged. Spontaneous labor and vaginal delivery at term	Mother and baby were healthy	Unknown (6)
40	33	Abdominal pain, nausea, vomiting	+	CT	Surgery	Mother and baby recovered	9,10 (7)
30	37	Abdominal pain	+	CT	Surgeryand eight hours postoperatively preterm labor	Mother recovered and the baby in the neonatal intensive care unit	0,2 (8)
23	29	Abdominal pain, nausea, vomiting	+	CT	Surgery, the patient was discharged.cesarean section at 36 weeks	Mother and baby recovered	Unknown (9)

Physical examination showed a pregnant abdomen, which was consistent with the gestational age. The patient had total abdominal pain, mainly in the lower abdomen, with tenderness and rebound pain. She had no noticeable uterine contractions, pain, or feelings of tightness. The cervix was closed.

Ultrasound testing of the foetus and the placenta was normal. Antepartum testing was also normal. Foetal surveillance was normal, and there were no obvious uterine contractions.

The patient was not considered to be in preterm labour. The cause of her abdominal pain was investigated, and acute gastroenteritis was considered. When she arrived at our inpatient department, we did not use dexamethasone considering that there was no uterine contraction pain.

Four hours after admission (at approximately 21:30), the patient felt increased pain in her left lower quadrant. She had total abdominal pain, mainly in the left lower abdomen, with tenderness and rebound pain. Strong, regular contractions were occurring every 3 min (**Figure 1**), and we started medication to prolong the period of gestation as soon as possible. Dexamethasone was administered to enhance foetal lung maturity, and intravenous tocolysis with ritodrine was started. Intravenous cefuroxime sodium was used to prevent infection.

The white blood cell count was 16,530, and the percentage of neutrophils was 86.20%. Procalcitonin, interleukin-6, C-reactive protein, pancreatic amylase, and pancreatic lipase levels were normal. As the patient's abdominal pain worsened, we examined the routine blood and infection indicators again. The white blood cell count was 20,670, and the percentage of neutrophils was 90.30%. Procalcitonin was 0.03 ng/ml, interleukin-6 was 44.90 pg/ml, and C-reactive protein was 7.90 mg/L. Computed tomography (CT) examinations are associated with ionizing radiation and are not advised in pregnancy, which could have a negative effect on the foetus, mainly depending on the the absorbed radiation dose and the gestational age at the time of exposure. However, CT examination may improve the diagnosis accuracy in the acute abdomen, especially intestinal obstruction and appendicitis. The patient was informed of the advantages and disadvantages of CT examinations. With the patient's permission, we immediately

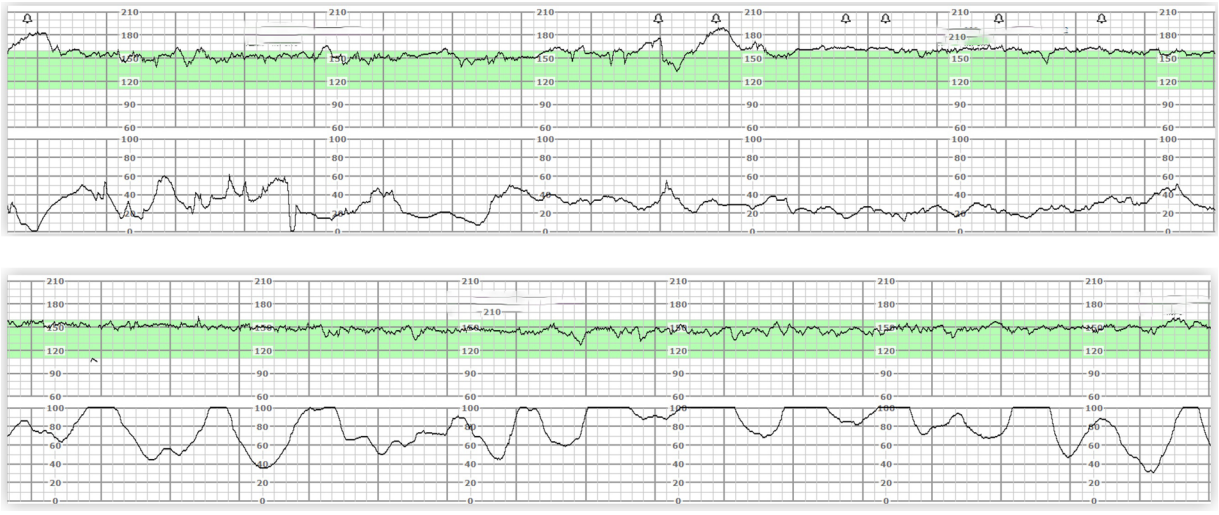

FIGURE 1
Electronic fetal monitor on admission and fetal monitor with contractions.

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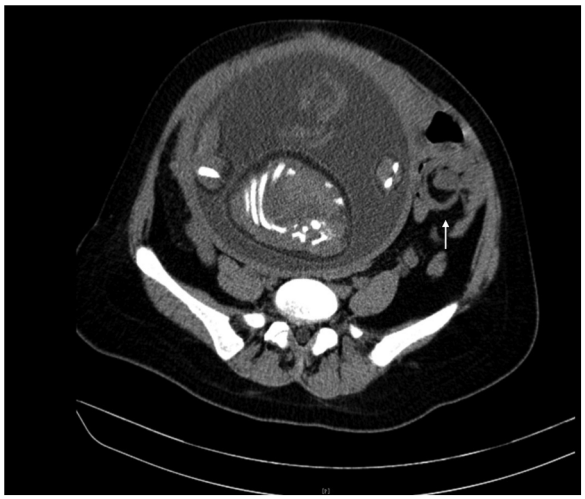

FIGURE 2
The left lower abdominal part of the small intestine was in a vortex shape in CT.

contacted the imaging department to perform B-ultrasound and CT examination. CT examination showed that the left lower abdominal part of the small intestine was in a vortex shape, and the local intestinal lumen was dilated. The intestinal inflammation was distinguished from the incomplete small intestinal torsion (Figure 2). No obvious abnormalities were found in the liver, gallbladder, spleen, pancreas or ureter.

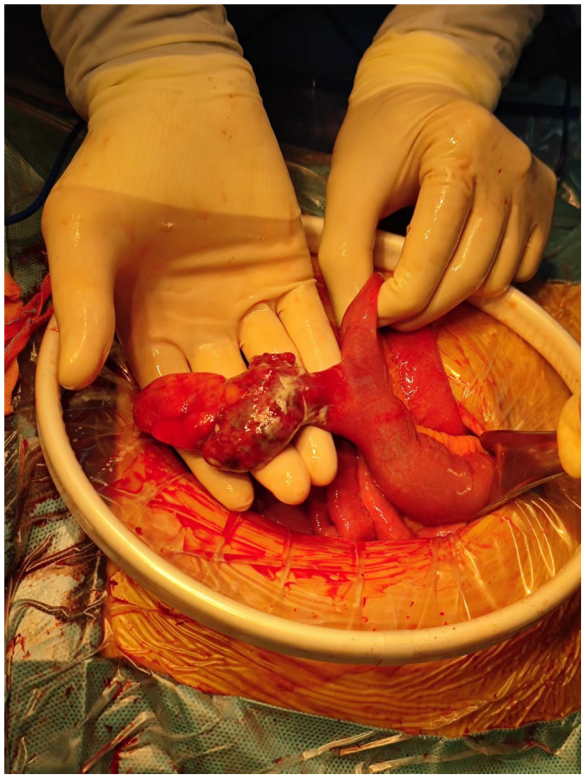

FIGURE 3
The MD was found during the surgery.

The next morning, the patient continued to feel abdominal pain, and she presented obvious tenderness and rebound pain, which showed peritonitis. We consulted radiologist and surgeon and they considered that the patient could have volvulus. The surgeon suggested that exploratory laparotomy be performed. Due to the large size of the pregnant uterus, which would obstruct the surgical field of view, combined with the gestational stage, the surgeon recommended emergency caesarean section in obstetrics, and the surgeon would assist in the exploration. The complete 10 mg dexamethasone injection was empirically administered before the operation.

We performed a caesarean section. The Apgar score at 1, 5, 10, 15 and 20 min was 10, 5 (each item was deducted one point), 9 (reflex irritability was deducted one point), 9 (reflex irritability was deducted one point) and 9 (reflex irritability was deducted one point), respectively. The foetus looked healthy and got full score at 1 min. However, the heart rate, respiratory effort, muscle tone, reflex irritability, and color from the foetus were not the best, so the foetus got 5 points when 5 min. Subsequently, the foetus was rescued by keeping warm and positive pressure ventilation by mask resuscitation bag. And then the foetus got 9 points because the reflex irritability was not the best after rescue. The foetus was finally transferred to the neonatology department. During the operation, the surgeon explored the small intestine MD, with a 360° twist and local necrosis without perforation (Figure 3). The MD was removed and sent for pathological examination, which showed acute inflammatory changes (Figure 4). Finally, the mother and the foetus recovered.

Discussion

Early diagnosis of acute abdomen in obstetrics is of great significance to improve the life and health of mothers and foetuses. Common obstetrical acute abdomen includes digestive inflammatory diseases, such as appendicitis, acute cholecystitis,

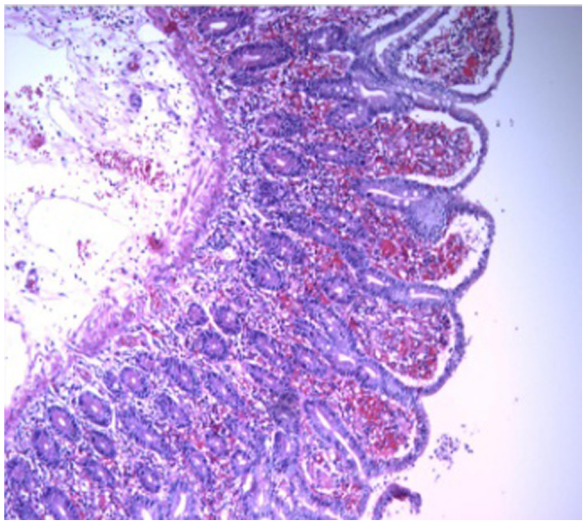

FIGURE 4
Histopathological findings confirmed a MD.

acute pancreatitis, and intestinal obstruction. In addition, urinary calculi and torsion of the ovarian cyst pedicle are also seen in the hospital. However, MD is rare. In this study, we reported pregnancy-complicated MD volvulus, which attracted our attention to the diagnosis of obstetrical acute abdomen. When we managed the acute abdomen, we could also consider MD.

MD is the most common anatomic abnormality of the gastrointestinal tract, resulting from the failure of the omphalomesenteric duct to involute during the 5th to 7th weeks of gestation (2) and it has been described as the "rule of twos": prevalence of 2% in the population, twice as common in men than in women, located 2 feet from the ileocecal valve, and can be 2 inches wide and long (10). MD is usually asymptomatic, and only 2%–4% of people become symptomatic, usually in children (11). A small number of cases can be diagnosed accidentally by an operation or imaging investigation (12). **Table 1** illustrates that most cases were diagnosed at emergency surgery. Symptomatic patients with MD present clinical features, such as obstruction of the small bowel, painless bleeding from the rectum, and signs of peritonitis, and common symptoms include vomiting, abdominal pain, fever, and bloody stools (13). Abdominal pain is a very common symptom, whereas nausea and vomiting were also observed. Symptomatic MD during pregnancy is an extremely rare event. There are no more than 40 cases reported so far since 1949, with 22 complicated by perforation (7).

Our patient presented primarily with abdominal pain, which became predominantly left lower abdominal pain, and eventually developed peritonitis. The first case presented with right lower abdominal pain reminiscent of acute appendicitis, with subsequent finding of MD at surgery. In fact, appendicitis could be the most common surgical pathology in the acute abdomen, but some rare diseases should be also considered. MD should not be neglected as one of the differential diagnoses of acute abdominal complaints in pregnancy.

Doctors find it difficult to diagnose MD-complicated pregnancy because it can present unspecific symptoms, such as abdominal pain, nausea, vomiting, and obstipation, which overlap with other conditions and can also occur physiologically during pregnancy. Moreover, moderate leucocytosis can be normal for pregnant women but indicates inflammation in the population without pregnancy, making it more difficult to perform timely evaluations. During pregnancy, symptomatic MD should be distinguished from obstetric diseases such as preterm labour, placental abruption or chorioamnionitis (6).

Ultrasonography is a common radiological investigation in the pregnant patient presenting with an acute abdomen (14). Ultrasonography is not of great importance for adults, but it is of value in paediatrics because it avoids radiation exposure, especially having a higher sensitivity in cases of complications (15). MRI imaging are largely perceived as safe for pregnant patients. It has a higher sensitivity and specificity in the diagnosis of appendicitis in pregnant women (16). However, MRI could not be the first choice because of the duration of scan and resource availability, especially in emergency conditions. Technetium-99 m(99mTc) pertechnetate scintigraphy is regarded as a relatively good diagnostic tool, particularly in children, while lower in adults (17). The scan could be considered if MD is suspected.

CT is common, but doctors can easily overlook MD, which could be considered a small intestinal loop without the presence of complications (18). When MD is accompanied by complications, CT is the best imaging study (19). Magnetic resonance is not of great value in the diagnosis of MD even if complications are present (20). This radionuclide scan has a sensitivity and specificity of 85% and 95% in children, respectively, but its sensitivity and specificity are not as high in adults (10). Ideal diagnosis is by upper GIT contrast follow through or just suspicion. Moreover imaging can be difficult to interpret and US or an abdominal x-ray would have probably been enough. The interpretation of images could be easier by artificial intelligence one day, which brings us more convenience (21). MD is usually diagnosed by exploratory laparoscopy in cases of complications (22).

In our report, CT showed the "whirlpool sign", indicating small bowel volvulus. Combining CT results and peritonitis, the surgical chief thought it was more likely to be small bowel volvulus and suggested exploratory laparoscopy, by which we found MD complicated by volvulus.

The mainstay of management for symptomatic Meckel's patients is surgical intervention. In the asymptomatic patient, a conservative approach is well justified giving the rarity of complications (23). Every patient in **Table 1** presented with abdominal pain and had to undergo surgery. The mode of delivery was either vaginal delivery or cesarean section, which may occur at the time of surgery for the MD, resulting in preterm births requiring neonatal intensive care. For the pregnant with MD, the trimester of pregnancy and foetus mortality should be considered when deciding whether and when to do an operation. The risks and benefits must be weighed against each other.

Many diseases can lead to acute abdomen, while MD is a rare cause of acute abdomen. CT is valuable for the suspicious diagnosis of MD accompanied by symptoms. When managing the acute abdomen, we must not forget the possibility of MD. For the pregnant woman with symptomatic MD, surgery is the preferred mode of management.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics Statement

Written informed consent was obtained from the patients for publication.

Author contributions

YH: was responsible for writing the first draft of the manuscript. LW: contributed to the data acquisition of the

article and revising it critically for important intellectual content. WC: was responsible for critical review of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2023.1051158/full#supplementary-material.

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Individualized conservative therapeutic strategies for adenomyosis with the aim of preserving fertility

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Adenomyosis is a diffuse or localized organic disease caused by benign invasion of endometrial glands and stroma into the myometrium. It is a common disease that seriously affects reproductive health of women in childbearing age. Due to the unknown etiology and pathophysiological mechanism, and the lack of unified diagnostic criteria and effective treatment methods, total or subtotal hysterectomy has become a radical treatment for adenomyosis, which will lead to the complete loss of fertility. With the continuous exploration of the treatment to adenomyotic patients who have infertility or fertility intentions, new drugs, surgical methods and treating concepts appears. Adopt individualized conservative therapeutic strategies for patients with different conditions, preserve the uterus as much as possible and protect the patient's fertility, which will play an important role on the follow-up assisted reproductive treatment and long-term management of adenomyosis.

KEYWORDS

adenomyosis, individualized treatment, uterus sparing operation, levonorgestrel-releasing intrauterine system, gonadotrophin releasing hormone agonist

1. Introduction

Adenomyosis is a benign invasion of endometrial glands and stroma into the myometrium, causing myofibrillar connective tissue hypertrophy and hyperplasia, and forming diffuse or localized lesions of the uterus (1). Its main clinical manifestations are progressive dysmenorrhea, uterine enlargement, abnormal uterine bleeding (including increased menstrual volume and prolonged menstrual cycle) and infertility (2). Its occurrence in the infertility population can reach to more than 30%, and it seriously affects the patients' quality of life. As adenomyosis is more common in women of childbearing age, it has gradually become one of the important clinical problems impairing human fertility, and its incidence rate range from 5 to 70% (3). Severe adenomyosis may be associated with adverse pregnancy and delivery outcomes (4).

1.1. Brief introduction of the pathogenesis and diagnosis of adenomyosis

The pathogenesis of adenomyosis is an important basis for treatment, but it has not been fully clarified. There are two main hypotheses about the pathogenesis of adenomyosis (5). One is the endometrial metaplastic hypothesis: adenomyosis lesions are generated directly by the differentiation of ectopic Mullerian tube residual cells, especially pluripotent stem cells with embryonic pluripotent (6). This hypothesis can partly explain the reason why many unmarried young women without pregnancy suffer from adenomyosis.

The other is the endometrial metastatic hypothesis, which believes that the enhancement and disorder of endometrial peristaltic waves, intrauterine infection (including Mycobacterium tuberculosis) or surgical procedures lead to the damage of endometrial-myometrial interface, namely the endometrial myometrium junction zone (JZ); then the glandular cells and stromal cells in the endometrium pass through the endometrial basal layer at the damaged site and invade the myometrium (7, 8). Endometrial stem cells may be recruited and self-repairing mechanism may be initiated in the local lesion. At the same time, the lesion can induce immune imbalance and aseptic inflammation, with increasing proglandin E2 (PGE2), proglandin H2 (PGH2), cyclooxygenase-2 (COX-2) and transforming growth factor β1 (TGF-β1), vascular endothelial growth factor (VEGF) and other factors (5). The increased aromatase activity promotes the synthesis of estradiol, which will up-regulate oxytocin and its receptor, as well as enhance peristalsis and damage of the endometrium (9). In this way, a vicious circle will be created, which eventually caused the cracking of the myometrium, endometrial basal cells invading into the myometrium, and the formation of adenomyosis lesions locally. This hypothesis can explain the clinical manifestations of elevated estrogen, menstrual abdominal pain, and increased menstruation in patients with adenomyosis (5).

In addition, there are other hypotheses, such as the hypothesis of retrograde menstruation, mesothelial metaplasia, etc. (6, 10). So far, no single hypothesis can fully explain all the pathological mechanisms and clinical manifestations of adenomyosis. Recently, investigations on the relationship between colors of human iris and hair and the characteristics of endometriosis may provide new inroads into the molecular aspects of the pathological mechanisms of these complex diseases (11).

At present, there is no consensus on the diagnostic criteria of adenomyosis by imaging methods. The criteria for the diagnosis of adenomyosis based on transvaginal ultrasonography (TVUS) images developed by the Federation International of Gynecology and Obstetrics (FIGO) in 2018 included eight ultrasound features (12, 13): asymmetric thickening of the myometrium, cystic lesions of the myometrium, island hyperechoic signals, fan-shaped shadows, linear or punctate echoes of the endometrium, streaked blood flow signals passing through the lesions, irregular shape and discontinuous JZ. If there are 2 or more of the above signs, the diagnosis can be made in combination with the patient's clinical manifestations.

MRI features of adenomyosis are of great significance for diagnosis (13, 14). On T2-weighted imaging, localized adenomyosis showed ovoid, irregular or quasi-circular mass in the myometrium, with unclear boundary, low signal similar to the JZ, and scattered dotted or flaky high signal in the lesion, showing cystic expansion or hemorrhage in the lesion. Diffuse adenomyosis showed equal signal on T1-weighted image (T1WI), and dotted high signal in some lesions of T2WI showed that JZ was damaged, showing diffuse thickening. When the thickness of JZ > 12 mm, adenomyosis was highly suspected. If the thickness of JZ is 8–12 mm, combined with high signal spots or irregular boundary, it is proposed to be diagnosed as adenomyosis. Of course, pathological examination through surgery or biopsy is the gold standard for the diagnosis of adenomyosis.

2. Individualized oral therapies for adenomyosis

The general therapeutic principles to be followed in clinical practice include reducing and removing lesions, relieving and eliminating pain, improving and promoting fertility, and reducing and avoiding recurrence. Adenomyosis has been regarded as a chronic disease requiring long-term management (15). Most premenopausal women need to receive long-term drug treatment, even after conservative surgery or interventional therapy (16). The individualized treating plan should be made according to the patient's age, symptoms, ovarian reserve, severity of disease, fertility desire and previous treatments. The main purpose of individualized treatment plan is to solve the problems including chronic pelvic pain, secondary dysmenorrhea, excessive menstruation and infertility.

2.1. Non-steroid anti-inflammatory drugs

For patients with the main symptom of pelvic or menstrual pain, non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used if the pain is mild, no fertility requirements or the menopause is approaching. NSAIDs are cyclooxygenase inhibitors, which can reduce the synthesis of prostaglandins in the endometrium and relieve dysmenorrhea (17). However, it cannot prevent the progression of endometriosis and adenomyosis. Adenomyosis relapses easily after NSAIDs withdrawal, and about 18% of patients have no response to NSAIDs (17, 18). Therefore, NSAIDs, such as ibuprofen, is usually used in combination with other treatment methods. It should be noted that long-term use may result to adverse reactions such as peptic ulcer, liver and kidney injury (19).

2.2. Compound oral contraceptives

Compound oral contraceptives (COC), such as drospirenone and ethinylestradiol tablets or cyproterone acetate and ethinylestradiol tablets, can reduce the amount of menstruation and relieve dysmenorrhea by inhibiting follicular development and ovulation, reducing estrogen level, inhibiting endometrial proliferation, and promoting endometrial atrophy (19, 20). COC is an important second-line treatment for menorrhagia patients due to adenomyosis, especially for those who need contraception (20). However, because COC has the potential to increase the risk of venous thrombosis and pulmonary embolism, patients over 40 years old or with high-risk factors (such as hypertension, diabetes, thrombosis and smoking history) should be very cautious.

2.3. Androgen derivatives

Androgen derivatives including danazol, gestrinone, etc., can lead to endometrial atrophy through double effects (21). On one hand, they inhibit the secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH), and inhibit ovarian synthesis of steroid hormones (16). On the other hand, they combine with estrogen and progesterone receptors of the endometrium, and finally cause temporary amenorrhea in patients (22). Androgen derivatives have certain effects on dysmenorrhea symptoms and abnormal menstruation (21). However, there is a problem of recurrence after drug withdrawal, and the incidence of androgen like adverse reactions, such as acne and seborrheic dermatitis, weight gain and liver injury.

Mifepristone is a progesterone receptor antagonist with high affinity. It is a derivative of 9-demethyltestosterone, which can be used to terminate pregnancy, soften the cervix, and also cause amenorrhea (23). There have been some studies on the short-term use of low-dose mifepristone in the treatment of adenomyosis with leiomyoma, which has a significant effect on the relief of dysmenorrhea (19). Long term use of mifepristone can result in continuous stimulation of the endometrium by estrogen, so its safety needs further verification.

2.4. Synthetic progesterones

Dienogest is a new generation of synthetic progesterone, which has high affinity with progesterone receptor, and has little effect on androgen, glucocorticoid and mineralocorticoid receptor (24). Therefore, it has little effect on organ function and metabolism. Dienogest moderately inhibits the hypothalamus-pituitary-ovary (HPO) axis, and moderately reduces the estrogen level and endometrial proliferation, which prevents the expansion of uterine lesions. The incidence of perimenopausal symptoms after long-term use is low. At the same time, dienogest has anti-inflammatory and anti-angiogenesis effects, as well as promoting the reduction of nerve growth factor expression and nerve fiber density in tissues, which can effectively prevent recurrence and relieve pain (25). Dienogest is mainly suitable for the patients who are in or near the perimenopause with pelvic pain. In addition, the number of invasive NK cells in the endometrial layer increased after dienogest treatment, which may be conducive to the follow-up assisted reproductive treatment of patients with infertility (25, 26). Common adverse reactions include irregular bleeding, breast discomfort, headache, etc., so patients with adenomyosis accompanied by menorrhagia and anemia should be cautious.

The molecular structure of dydrogesterone is similar to that of natural progesterone, but its activity is much higher. Because it has no androgen, estrogen and mineralocorticoid like effects, dydrogesterone does not inhibit ovulation and has no inhibitory effect on normal endometrium. The patient can be pregnant during the medication of dydrogesterone, so it is especially suitable for adenomyosis patients with a recent pregnancy plan (27). Dydrogesterone is rapidly absorbed by oral administration with short half-life, and has obvious effect on inhibiting endometrial proliferation without causing low estrogen symptoms or affecting lipid metabolism and blood system (28). Thus it is safe for long-term use and suitable for patients above 40 years old, or those with high risks of metabolic and thrombotic diseases. Dydrogesterone is also often used in combination with other treatments (29). Due to the widespread use of didroxyprogesterone in other fields of gynecology and reproductive medicine, patients with adenomyosis have higher acceptance and compliance with it (29, 30).

2.5. Traditional Chinese medicine

Traditional Chinese medicine has a long history in dealing with various symptoms of adenomyosis. From the perspective of traditional Chinese medicine, the basic pathogenesis of adenomyosis is due to Blood-stasis blocking Chong-ren and Bao-gong, which belongs to internal syndrome (31). The disease location of adenomyosis is in Xia-jiao, so the general treatment principle is to promote blood circulation and remove Blood-stasis (Blood-stasis, Chong-ren, Bao-gong and Xia-jiao are all anatomical and pathological terms of traditional Chinese medicine). Traditional Chinese medicine therapies, such as Guizhi Fuling Capsule, Danhuang Quyu Capsule, Zhitong Huazheng Capsule, Sanjie Zhentong Capsule, Shaofu Zhuyu Decoction Modified, as well as catgut embedding, acupuncture and acupoint application, all have certain effects on relieving the clinical symptoms of adenomyosis (31, 32).

Traditional Chinese medicine is not only beneficial to the treatment of clinical symptoms of adenomyosis, but also provides a completely individualized treatment concept more importantly (33). In fact, traditional Chinese medical treatment is highly individualized for all diseases, including adenomyosis. The types of Chinese herbal medicine and measures used vary from person to person, time to time, and place to place. There is no unified treatment standard, which is instructive for the diagnosis and treatment in modern medicine. There will be a bright future to treat adenomyosis with the concept of combining traditional Chinese and modern medicine.

3. Individualized non-oral drugs for adenomyosis

3.1. Gonadotropin-releasing hormone agonist

Gonadotropin releasing hormone agonist (GnRH-a) is an category of GnRH analog, whose affinity with GnRH receptor is much higher than that of natural GnRH (34). Long acting GnRH-a binds to a GnRH receptor in the pituitary gland to produce a transient increase in gonadotropin. Its continued binding to the receptor with subsequent movement into the pituitary cell prevents the pituitary gland from responding to endogenous GnRH. In this way, GnRH-a thoroughly inhibits the HPO axis of patients with adenomyosis and induces a sharp decrease in ovarian synthetic steroids, endometrial atrophy, decreased bleeding and even temporary amenorrhea (35). Long-acting GnRH-a can reduce uterine volume of patients with adenomyosis, and dysmenorrhea is also significantly relieved. However, continuous use for several months may lead to perimenopausal symptoms and osteoporosis, and estrogen should be added as appropriate. Because of the high price and obvious recurrence after drug withdrawal, GnRH-a is rarely used alone (36). Although GnRH-a is applicable to a wide range of patients, it is generally used as a pretreatment for other long-term treatments (35).

3.2. Levonorgestrel releasing intrauterine system

After levonorgestrel releasing intrauterine system (LNG-IUS) is implanted into the uterus, it can sustain a constant sustained release of 20 μg per day for 5 years. LNG-IUS mainly acts on the endometrium directly, and inhibits the synthesis of estrogen receptor in the endometrium which induces the sensitivity of the endometrium to estradiol and strongly antagonizes the proliferation of the endometrium (37). Therefore, it can be used not only for contraception, but also to treat adenomyosis, reduce the amount of menstruation, shrink the uterine volume, and relieve dysmenorrhea. LNG-IUS is effective for adenomyosis with dysmenorrhea and menorrhagia, especially recommended for the latter (38, 39). LNG rarely enters the peripheral circulation, so there are few systemic side effects except for minor vaginal bleeding and amenorrhea. Thus LNG-IUS can also be used for patients with a history of systemic diseases (such as hypercoagulable state, liver injury) or high risk, but patients must be fully informed of the advantages and disadvantages before use (20). LNG-IUS is applicable to adenomyosis patients who wish to conserve the uterus and fertility. As uterine cavity deformation, poor closure and excessive menstruation are common in adenomyosis patients, LNG-IUS is easy to fall off or move down (40). Accurate positioning under hysteroscopy, fixation to uterine wall, using GnRH-a pretreatment and other measures will help reduce the rate of LNG-IUS shedding and save medical expenses.

Xiao et al. found that LNG-IUS had a good therapeutic effect on patients with small lesions or small uterine volumes, while it had a poor therapeutic effect on patients with large lesions or large uterine volumes, or even no effect (41). This suggests that LNG-IUS is selective for lesion size in the treatment of adenomyosis, that is the phenomenon of 'lesion threshold' for LNG-IUS to effectively treat adenomyosis. This may be related to the pharmacological mechanism that LNG directly acts on the endometrium and diffuses to the myometrium. A large number of clinical data shows that the lesion threshold for LNG-IUS to take effect is the lesion range (LR: mean diameter of adenomyoma lesions or thickness of unilateral uterine muscle wall) ≤ 40 mm, and the corresponding threshold of uterine volume is (140.0 ± 35.4) ml. The lesion threshold for marked therapeutic effect is LR < 30 mm, with corresponding uterine volume (117.4 ± 34.1) ml, so that LNG-IUS had the most obvious effect in relieving symptoms and reversing the condition. When LR is $30 \sim 40$ mm, LNG-IUS can reduce menstruation and dysmenorrhea, but the effect on reducing the uterine volume is not satisfactory. When LR > 40 mm, LNG-IUS alone has nearly no effect on reducing symptoms (41, 42). Lee et al. also showed that the effect of LNG-IUS on adenomyosis was poor if the uterine volume was >150 ml (43). We hope that there will be more *in vivo* and *in vitro* researches on the LR of LNG-IUS in the future, which will provide a research basis for the wider clinical application of LNG-IUS.

3.3. Other drugs

The main component of subdermal implant contraceptives is also synthetic potent progestogen which can achieve a theoretical effect similar to LNG, but its clinical application is limited (44).

4. High intensity focused ultrasound

High intensity focused ultrasound (HIFU) is a kind of physical therapy, which has the advantages of no operation, no bleeding, no ionizing radiation and repeatability (38). It is a more accurate treatment for localized adenomyosis with good effect, and preserves the integrity of the uterus. It is suitable for patients who have fertility planning and desire to conserve the uterus. The principle of HIFU ablation is to focus the ultrasound on the target tissue through the instrument. The thermal effect, cavitation effect and other physical effects of the ultrasound instantly raise the temperature of the target tissue to $65°C \sim 100°C$, and cause tissue protein denaturation, coagulative necrosis. The tissue finally is dissolved, absorbed, calcified or fibrotic (41). With the continuous improvement of technology, the popularity and indications of HIFU treatment are gradually expanding, but it is easy to recur. In most cases it needs to be used in combination with other methods (45).

5. Conservative surgical management for adenomyosis

The uterus is not only a reproductive organ, but also plays a role in maintaining the normal anatomical structure of the pelvic floor as well as the blood supply of pelvic organs, especially ovary. Radical surgery, including total hysterectomy or subtotal hysterectomy, is the most thorough and effective method to treat adenomyosis, but it will deprive the fertility and have adverse effects on patients' pelvic floor function, ovarian function, sexual life quality and self-cognition (46). Therefore, more and more attention has been paid to the conservative surgery.

Uterine artery embolization (UAE) and laparoscopic uterine artery occlusion on patients with adenomyosis both aim to block the blood supply of the lesion, but may lead to obstruction of ovarian blood supply or endometrial necrosis, resulting to secondary infertility (47). Transcervical endometrial resection (TCER) can lessen the symptoms of adenomyosis but cannot interfere with its progress. TCER removes the material basis of embryo implantation, so it cannot be used for patients with fertility requirements (48).

Resection of uterine lesion (RUL) is a very complex and challenging operation, and to achieve a balance between removing adenomyosis and retaining normal myometrium and the integrity of the uterus (49). RUL is often applied to adenomyosis patients with fertility requirements or young age. Therefore, there is no completely rigid surgical procedure, and flexible operations should be carried out according to factors such as the shape of the uterus, the size and location of the lesions. Common operational methods include wedge resection, asymmetric resection, and partial resection of muscle wall lesions (50). The repair of uterine myometrium and the reconstruction of uterine body are crucial for the uterus to withstand pregnancy, including H-shaped and, U-shaped suture, muscle overlapping-flap suture and triple-flap suture proposed by Osada, etc. (51, 52). In recent years, Xiao et al. have created the major uterine wall resection and reconstruction of the uterus (MURU) on the basis of RUL, which provides a new surgical method for patients with severe adenomyosis to preserve

the uterus (42). MURU destroys the structure of the uterus, and the uterine scar is large with the high risk of uterine rupture during pregnancy. Therefore we are modifying the procedures to meet the fertility requirements of patients after operation. Of course, multi-center clinical research and more verification are needed before large-scale promotion of MURU. However, the recurrence, low natural pregnancy rate and the risk of uterine rupture during pregnancy are the main problems after conservative surgery (53). It is very important to treat as early as possible and develop an individual combined therapy to preserve the uterus according to the degree of adenomyosis.

6. Individualized combined therapy

Different therapies for adenomyosis have their own advantages and disadvantages, which causes great confusions for doctors and patients and probably leads to insufficient or excessive treatments (Table 1). Xiao et al. proposed a personalized therapeutic strategy based on the concept of grading, which provides a new option for patients with adenomyosis who wish to preserve fertility (41, 42). It divides adenomyosis into three grades according to the LR: mild (LR ≤ 30 mm), medium (LR between 30-40 mm) and severe (LR ≥ 40 mm). The corresponding processing methods for each grade are as follows:

TABLE 1 The characteristics and application of individualized fertility preserving treatments for adenomyosis.

Classification of treatments		Typical drugs	The characteristics and applications	Special notes
Individualized oral therapies	NSAIDs	Ibuprofen	Reliese the pelvic or menstrual pain; Used in combination with other treatment methods	18% of patients no response; Long-term use may result to peptic ulcer, liver and kidney injury, etc.
	COC	Trospirone ethinylestradiol tablets; Ethinylestradiol cycloproterone tablets	Reduce menstruation; Relieve dysmenorrhea; Inhibit endometrial proliferation; Fit for contraception	Increase the risk of thrombosis and embolism; Use with cautions for patients over 40-y or with high-risk factors
	Androgen derivatives	Danazol; Gestrinone; Mifepristone; etc	Inhibit the secretion of gonadotropins and sex hormones and induce temporary amenorrhea	Recurrence after drug withdrawal; Androgen like adverse reactions; Security risk for long-term use
	Synthetic progesterones	Dienogest; Dydrogesterone	Inhibit HPO axis, Reduces the estrogen level and endometrial proliferation, Relieve pain, Fit for perimenopause patients	Adverse reactions include irregular bleeding, breast discomfort, headache, etc.,
	Traditional Chinese medicine	Guizhi Fuling Capsule; Danhuang Quyu Capsule; Zhitong Huazheng Capsule; Sanjie Zhentong Capsule; Shaofu Zhuyu Decoction Modified	Promote blood circulation; Remove Blood-stasis; Relieving clinical symptoms	Provides completely individualized treatments
Individualized non-oral therapies	GnRH-a	Leuprorelin Acetate Microspheres For Injection	Thoroughly inhibit the HPO axis; Reduce ovarian synthetic steroids and uterine volume; Relieve pain	Long-term use leads to perimenopausal symptoms; Obvious recurrence after withdrawal; Used as pretreatment
	LNG-IUS	LNG-IUS	Act on the endometrium directly; Antagonize endometrial proliferation; Few systemic side effects	Easy to fall off or move down; Minor vaginal bleeding and amenorrhea
	Subdermal implant contraceptives	Levonorgestrel Silastic Implants	Similar to LNG-IUS	Limited clinical application
HIFU		–	The thermal and cavitation effect cause tissue protein denaturation and finally dissolution or fibrosis	A physical therapy with no operation; Fit for localized adenomyosis; Easy to recur

(Continued)

TABLE 1 (Continued)

Classification of treatments		Typical drugs	The characteristics and applications	Special notes
Conservative surgery	Uterine artery embolization; Laparoscopic uterine artery occlusion	–	Block the blood supply of the lesion in uterus	May lead to obstruction of ovarian blood supply or endometrial necrosis
	Transcervical endometrial resection	–	Lessen the symptoms of dysmenorrhea	Unable to prevent disease progression and damage fertility
	Resection of uterine lesion	–	Flexible operations according to the shape of the uterus, the size and location of the lesions; Include H-shaped, U-shaped, muscle overlapping-flap, triple-flap and Xiao's MURU suture	Recurrence, low natural pregnancy rate and risk of uterine rupture during pregnancy

(1) For patients of mild grade, the long-term management by LNG-US is the main method. If there are still symptoms such as dysmenorrhea after that, NSAIDs, progesterone and COC should be given. Remove LNG-US before receiving assisted reproductive therapy.
(2) For patients of moderate grade, GnRH-a can be used for 3–6 months firstly. If LR reduces to ≤30 mm, the patients should be treated according to the principle of mild grade. If LR does not reduce obviously, HIFU can be used for to reduce LR as combined treatment.
(3) For patients of severe grade, GnRH-a should also be used for 3–6 months firstly. RUL or modified MURU should be performed after GnRH-a, and LNG-US is placed into the uterine cavity during the surgery. Remove LNG-US before receiving assisted reproductive therapy.

This grading of adenomyosis is mainly based on the LR in imaging, which lacks evaluation of clinical symptoms of patients, and needs further development to be widely used in practice. Anyway, this grading strategy is a great promotion to the treatment of adenomyosis.

7. Conclusion

Adenomyosis is a disease that tends to occur in childbearing aged women. The treatments are diverse but lack specificity. The basic treating principles for the adenomyosis patients with fertility requirements should include protecting physical and mental health, preserving reproductive organs and functions. It is crucial to allow patients the full advantages of each method and choose an individualized strategy according to the grading and needs of each patient. Follow up should be insisted, and combined or continuous therapy should be used to relieve symptoms and prevent disease progression if necessary.

Author contributions

LH and YL determined the topic and write the manuscript. KL and JJ retrieved literatures. CZ made the table. CZ and YW analyzed data and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The accuracy of international and national fetal growth charts in detecting small-for-gestational-age infants using the Lambda-Mu-Sigma method

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Objective: To construct a national fetal growth chart using retrospective data and compared its diagnostic accuracy in predicting SGA at birth with existing international growth charts.
Method: This is a retrospective study where datasets from May 2011 to Apr 2020 were extracted to construct the fetal growth chart using the Lambda-Mu-Sigma method. SGA is defined as birth weight <10th centile. The local growth chart's diagnostic accuracy in detecting SGA at birth was evaluated using datasets from May 2020 to Apr 2021 and was compared with the WHO, Hadlock, and INTERGROWTH-21st charts. Balanced accuracy, sensitivity, and specificity were reported.
Results: A total of 68,897 scans were collected and five biometric growth charts were constructed. Our national growth chart achieved an accuracy of 69% and a sensitivity of 42% in identifying SGA at birth. The WHO chart showed similar diagnostic performance as our national growth chart, followed by the Hadlock (67% accuracy and 38% sensitivity) and INTERGROWTH-21st (57% accuracy and 19% sensitivity). The specificities for all charts were 95–96%. All growth charts showed higher accuracy in the third trimester, with an improvement of 8–16%, as compared to that in the second trimester.
Conclusion: Using the Hadlock and INTERGROWTH-21st chart in the Malaysian population may results in misdiagnose of SGA. Our population local chart has slightly higher accuracy in predicting preterm SGA in the second trimester which can enable earlier intervention for babies who are detected as SGA. All growth charts' diagnostic accuracies were poor in the second trimester, suggesting the need of improvising alternative techniques for early detection of SGA to improve fetus outcomes.

KEYWORDS

small-for-gestational-age, estimated fetal weight, growth chart, reference chart, fetal growth, INTERGROWTH-21st growth chart, Hadlock growth chart, WHO growth charts

Introduction

Small-for-gestational-age (SGA) refers to newborns with birth weights less than the 10th centile who may have a higher risk of adverse perinatal and long-term health outcomes due to fetal growth restriction (FGR) (1, 2). FGR refers to a fetus that fails to reach its genetically determined growth due to multiple factors, including maternal conditions, placental

insufficiency, or fetal-related causes. FGR is the main risk factor for stillbirth and the stillbirth rate (per 1,000 birth) increased from 4.2 to 9.2 if FGR remains undetected before delivery (3). FGR detection before birth is essential as the risk of adverse outcomes can reduce four-fold if proper antenatal care is given (4).

Current clinical standards in detecting SGA include fetal growth assessment *via* routine ultrasonography where fetal weight is compared with a population growth chart. The Hadlock chart is commonly accepted worldwide (5). Various fetal reference growth charts have been proposed by the INTERGROWTH-21st project (6), the NICHD Fetal Growth Study (7), and the World Health Organization (WHO) (8). Discussion on which growth charts should be adopted in the local cohort is ongoing because the choice of growth chart has profound implications on the clinical management of fetal growth assessment (9, 10).

Malaysia has 440 K live birth per year and 50 stillbirths rate per 10 K birth (11). The stillbirth rate due to FGR is 16.5 per 1,000 birth (12). The motivation to construct a national fetal growth chart is due to the increased stillbirth rate in Malaysia, leading to the failure to achieve the UN's' Millennium Development Goals (MDGs) of child mortality reduction and improvement of maternal health. Evidence has shown that fetal weight is greatly influenced by genetic and demographic factors (13–16). To date, Malaysia lacks a national fetal growth chart and is using international growth charts, which are created based on the Caucasian population (5), in fetal growth assessment which may underdiagnose SGA.

The first objective of this study is to investigate the diagnostic performance of various international growth charts in predicting SGA at birth. The second objective is to construct a national fetal growth chart using ten-year retrospective local data and compare its diagnostic performance in predicting SGA at birth with existing international growth charts.

Methods

Subjects

The study protocol was approved by the University of Malaya Medical Center, Medical Research Ethical Committee (MREC) with MECID.No: 2021329-9997. All the data involved in the current research project originated from Pusat Perubatan Universiti Malaya (PPUM), a government-funded medical institution in Kuala Lumpur, Malaysia. Prenatal data from May 2011 to Apr 2021 were extracted from the system. Scan records with missing values, pregnancy with multiparity, stillbirth, and consist of values that fall outside the range of three times the interquartile range were removed. Only one ultrasound measurement was used for each fetus. We have a total of 68,897 scans from May 2011 to Apr 2021. A total of seven features were extracted from the scan records and are described in **Table 1**. All ultrasound measurements were performed by sonographers certified by the Fetal Medicine Foundation.

TABLE 1 Description of features collected in prenatal data.

Feature	Description
Pregnancy ID	Identity code of the patient.
Gestational Age	Dating by last menstrual period or crump-lump length.
Biparietal Diameter (BPD)	A measurement of the diameter of the fetus's skull, measured on the axis plane of the fetus vertex, from one parietal bone to the other.
Head Circumference (HC)	A measurement of the circumference of the fetus's skull, measured on the axis plane of the fetus vertex, head-around of the fetus's skull.
Abdominal Circumference (AC)	A measurement of the circumference of the fetus's abdomen, measured on the transverse section through the upper abdomen.
Femur Length (FL)	A measurement of the long bone in the fetus's thigh, measured from the blunt end of the bone to the shaft.
Estimated Fetal Weight (EFW)	An estimation of the weight of the fetus based on ultrasonographic measurement using the Hadlock formula.

Outcome

Our primary outcome was to predict SGA at birth. We defined SGA at birth when the birth weight is less than the 10th centile, based on the INTERGROWTH-21st preterm and term birth weight chart (17, 18). If birth weight is above the 10th centile, it is defined as appropriate gestational age (AGA) at birth.

Development of fetal growth reference curves

We adopted the first nine-year datasets from May 2011 to Apr 2020 ($n = 67{,}063$ scans) to generate the fetal growth chart using the Lambda-Mu-Sigma (LMS) statistical method (19). The LMS method is an established method in creating reference charts (20–22). The LMS method summarizes the distribution of fetal biometrics by gestational age in three aspects, which are Lambda (L) which indicates the skewness of the distribution of fetal biometrics by Box-Cox transformation power, Mu (M) which indicates the Median of the fetal biometric, and lastly the Sigma (S) that indicates the coefficient of the variation of the fetal biometric. Nature smoothing spline function was applied to obtain the smoothed value of Lambda, Mu, and Sigma for each gestational age, these values were then fed into the equation as followed to calculate the percentile value in a particular gestational age:

$$C = M\,(1 + (L \cdot S \cdot Z))^{\frac{1}{L}} \quad (1)$$

where C is the unit value at a particular percentile level to be calculated; M, L, and S are the Mu (median), Lambda (skewness of distribution), and Sigma (coefficient of variation) as described previously; Z is the corresponding Z-Score of the percentile in a normalized distribution (e.g. for the value of percentile 2.5th, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 97.5th, Z will be substituted as −1.960, −1.881, −1.645, −1.282, −0.675, 0, 0.675,

and 1.282, 1.645, 1.881, 1.960). The generated unit value at a particular percentile using the LMS method was aggregated and presented as a fetal growth reference curved with intervals of one week by gestational age.

The difference between our LMS fetal growth chart and the growth chart from WHO (8), INTERGROWTH-21st (6, 23), and Hadlock (5) was compared using relative percentage difference (Equation 2).

$$\text{Relative \% Difference} = \left(\frac{\text{International Growth Chart Centile Value} - \text{LMS Centile Value}}{\text{LMS Centile}} \right) \times 100\% \quad (2)$$

Performance analysis of fetal growth reference charts in predicting SGA at birth

The 10th-year datasets (May 2020 to Apr 2021, $n = 1{,}834$ scans) were used to evaluate the accuracy of our fetal growth chart in predicting SGA at birth. Fetuses with EFW that fall below the 10th centile were predicted as SGA at birth while fetuses with EFWs above the 10th centile were predicted as AGA at birth.

The evaluation was divided into three parts. First, the performance of the local growth chart, generated using local data with the LMS method, in predicting SGA at birth was evaluated. Second, we analyzed the performance of the local growth chart in predicting SGA at birth in preterm and term infants. A preterm infant is defined as when an infant is born before the 37th week while a term infant is defined as when an infant is born after the 37th week (24). Third, we further analyze the performance of the chart in predicting SGA at birth using second and third-trimester data for term and preterm infants. Any data with gestational age between the 13th week and 27th week was identified as "second trimester" and data with gestational age more than or equal to 27th was identified as "third trimester".

The performance of the local growth chart and WHO (8), INTERGROWTH-21st (6, 23), and Hadlock (5) fetal growth charts in predicting SGA at birth were compared. The dataset is imbalanced as the number of SGA is much lesser than the number of AGA cases, balanced accuracy is used instead of accuracy (25). Balanced accuracy is the mean of sensitivity and specificity. Balanced accuracy, sensitivity, and specificity were reported.

Statistical analysis

Statistical analysis was performed to test if there were any significant differences between the AGA and SGA. For continuous variables, normality test was performed to check for data distribution. If data is normally distributed, Student T-test is used else non-parametric Mann-Whitney test is used for analysis. For categorical variables, chi-square test was performed to determine if there is a significant difference between AGA and SGA. The data were deemed significantly different if $p < 0.05$.

Results

Patients characteristics

Figure 1 shows the data distribution used to generate our fetal growth chart curves. In 2011, UMMC had just started using a proper electronic system for keeping patient records and thus the datasets in 2011 were limited and all of them were in 2nd trimester. Table 2 tabulates the patients' characteristics from May 2020 to Apr 2021, which was used for evaluating the accuracy of various growth charts in identifying SGA at birth. There are 781 newborns with 706 AGA and 75 SGA, defined using the birth weight of the infants. There were significant differences between AGA and SGA fetuses, where the occurrence of maternal hypertension, pre-eclampsia, gender, as well as the birth anthropometric measurements of birth weight, length, and head circumference differ. No significant differences were observed for maternal age, anemia, gestational age at birth, and APGAR score for 1 min and 5 min.

Fetal growth reference curves

Figures 2, 3 shows the reference charts for biparietal diameter, head circumference, abdominal circumference, femur length, and estimated fetal weight generated using the LMS method. Supplementary Tables S1–S5 show the centile estimations for completed weeks of gestation.

Fetal growth reference curves comparison

Figure 4 shows the relative percentage difference of the EFW centile curve between the local generated curve and the WHO, INTERGROWH-21st, and Hadlock centile curves. A positive percentage error indicates the percentile value of growth reference (WHO/ INTERGROWH-21st/Hadlock) is larger than the percentile value of growth reference developed in our study. In other words, the positive and negative percentage error representing fetal growth are over- and under-estimated, respectively, if international growth references (WHO/ INTERGROWH-21st/Hadlock) are adopted for fetal growth assessment in the local population.

In our study, we found that the discrepancy between our EFW chart and the WHO growth chart ranged from +18% to −10% across gestation, indicating an 18% of overestimation at early gestation and a 10% underestimation of fetus growth at late gestation. From Figure 4A, the WHO growth chart overestimated the FGR fetus growth (light grey line) and the

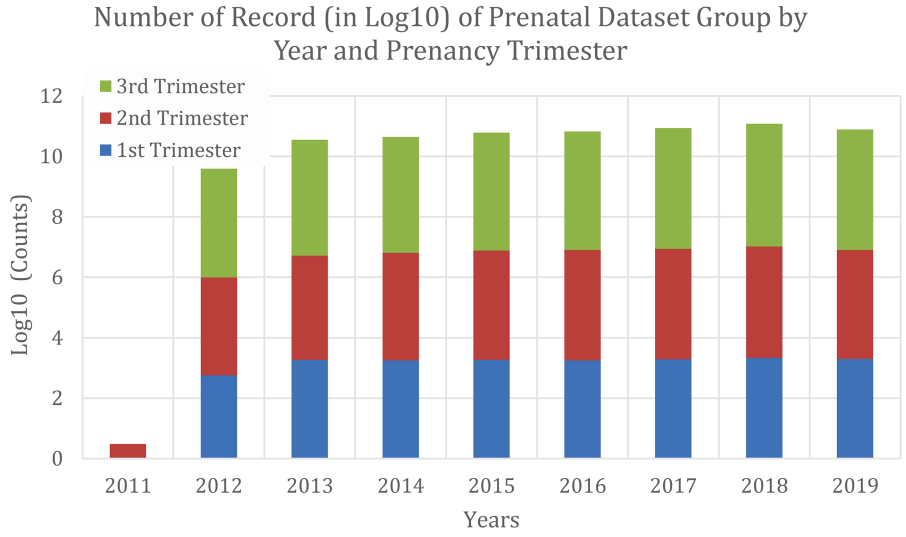

FIGURE 1
Data distribution from Apr 2011 to May 2020 that was used to generate local fetal growth chart curves.

overestimation of FGR fetus growth was 15% in the 15th week and dropped gradually to below 5% after the 23rd week. The percentage error for evaluating EFW below the 10th centile between our growth chart and WHO curve was small, approximately 0.56%, between 25th to 37th week.

The Hadlock curve exhibited a similar reducing trend of percentage error when compared to our local EFW curves. The percentage error was 16% in the 15th week and dropped to below 5% after the 25th week. The percentage error for evaluating EFW below the 10th centile from 25th to the 37th week between our growth chart and Hadlock curve was approximately 2.03%.

As there were no information available before the 21st week in the INTEGROWTH-21st chart, the comparisons were only made between the 22nd to 40th week. From Figure 4C, the INTEGROWTH-21st chart exhibited a negative discrepancy between the 22nd to 25th week, indicating that some of the fetuses may be misdiagnosed as AGA. The discrepancy increased to positive after the 25th week and declined around the 32nd week.

TABLE 2 Patient characteristics from May 2020–Apr 2021.

N = 781	AGA (*N* = 706)	SGA (*N* = 75)	*p*-value
Mother Age	34.16 ± 3.96	34.63 ± 3.88	0.301
Anemia	28 (4.0%)	6 (8.0%)	0.104
Hypertension*	58 (8.2%)	14 (18.6%)	0.003
Pre-eclampsia*	-	2 (2.7%)	<0.0001
Gestational Age at birth (week)			
Term	38.09 ± 0.91	38.10 ± 0.99	0.981
Preterm	35.64 ± 0.77	35.24 ± 1.09	0.105
Gender*			
Female	334 (47.3%)	46 (61.3%)	0.021
Male	372 (52.7%)	29 (38.7%)	
Birth weight (g)*	3091.86 ± 387.06	2341.93 ± 339.60	<0.0001
Birth length (mm)*	47.70 ± 2.13	45.02 ± 2.37	<0.0001
Head circumference at birth (mm)*	33.65 ± 1.84	31.75 ± 1.32	<0.0001
APGAR score (1 min)	8.81 ± 0.90	8.79 ± 1.15	0.552
APGAR score (5 min)	9.90 ± 0.70	9.85 ± 1.16	0.519

Values shown for continuous variables are mean and standard deviation while categorical variables are counts (percentage) *N*: Number of newborn.
*indicates $p < 0.05$.

Evaluation of fetal growth reference chart in general

Table 3 shows the results of each fetal growth reference chart in predicting SGA at birth. Based on the result, we noticed that our fetal growth reference chart generated using the LMS method achieved similar balanced accuracy (69%), as the WHO chart. The recall for both local and WHO charts were similar, achieving 42% and 43%, respectively. The INTERGROWTH-21st chart had the poorest performance with a balanced accuracy of 57% and 19% recall. All charts had similar specificity of 95%–96%.

To further understand the performance of each chart in predicting SGA, we performed another analysis by segregating SGA into preterm and term SGA (Table 4). Based on the result, we observed a similar pattern as observed in Table 3, where the WHO and our local chart achieved the highest accuracy in predicting SGA for both preterm and term infants, followed by the Hadlock and INTERGROWTH-21st charts. For preterm infants, *via* the LMS method, the WHO and local growth chart achieved balanced accuracy of 76% and recall of 65% in predicting SGA at birth. The Hadlock chart had slightly lower accuracy and recall as compared to the WHO and local charts. The INTERGROWTH-21st chart showed the lowest balanced accuracy of 63% and recall of 31% for preterm SGA. For term infants, the WHO chart depicted the highest balanced accuracy, with 66% and recall of 35% for SGA, followed by our local growth chart with 65% balanced accuracy and 34% recall. The INTERGROWTH-21st chart, again, showed the lowest

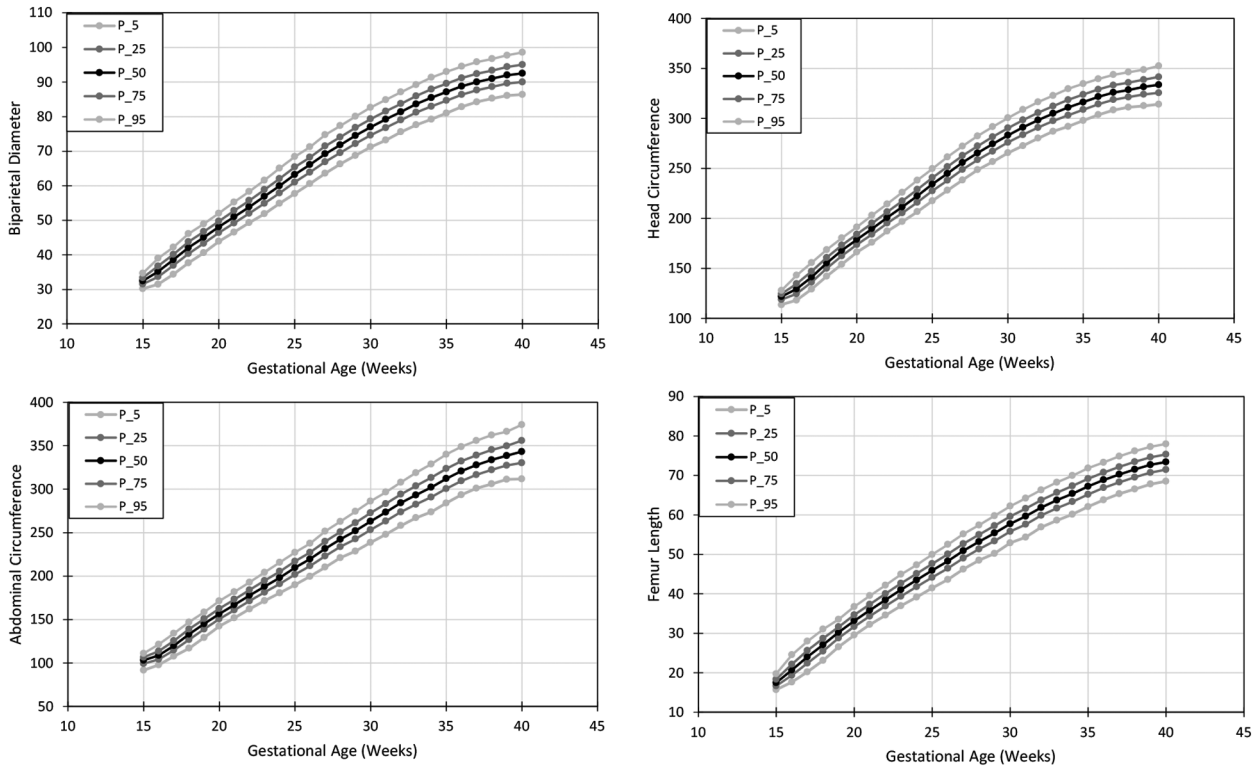

FIGURE 2
Local fetal growth reference charts for biparietal diameter, head circumference, abdominal circumference, and femur length using LMS method.

accuracy of 55% and recall of 14%. For preterm SGA, the INTERGROWTH-21st chart showed the highest specificity of 94%, followed by the Hadlock chart, with 90% specificity. The WHO and our local charts had slightly lower specificities, 88%. For the term SGA, all four charts showed similar specificity of approximately 96%.

Table 5 shows the results of various fetal growth charts in predicting term and preterm SGA in the 2nd and 3rd trimesters. Interestingly, although the INTERGROWTH-21st chart had the poorest performance in Tables 3, 4, it had the highest balanced accuracy when predicting SGA in 2nd trimester but dropped greatly in 3rd trimester (Balanced Accuracy: Preterm SGA: 75%

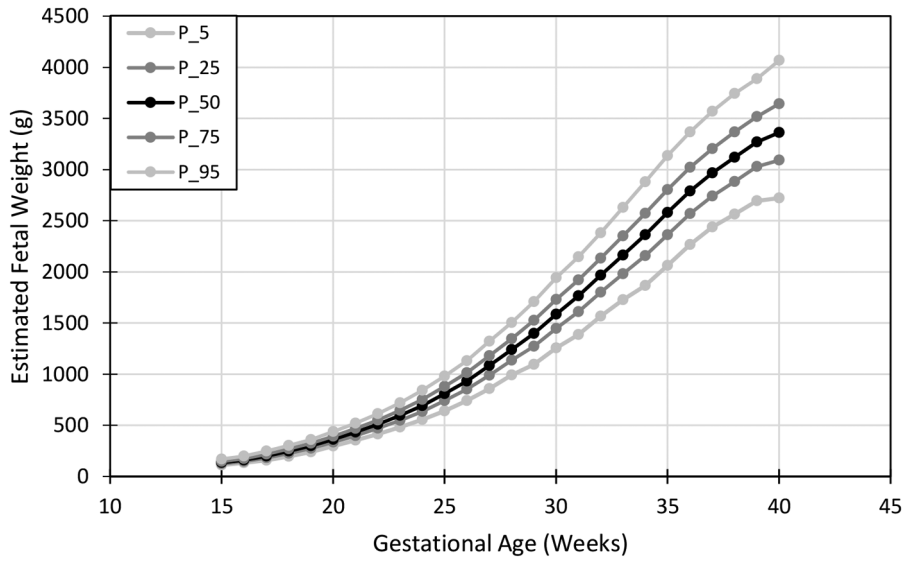

FIGURE 3
Local fetal growth reference curve for estimated fetal weight using LMS method.

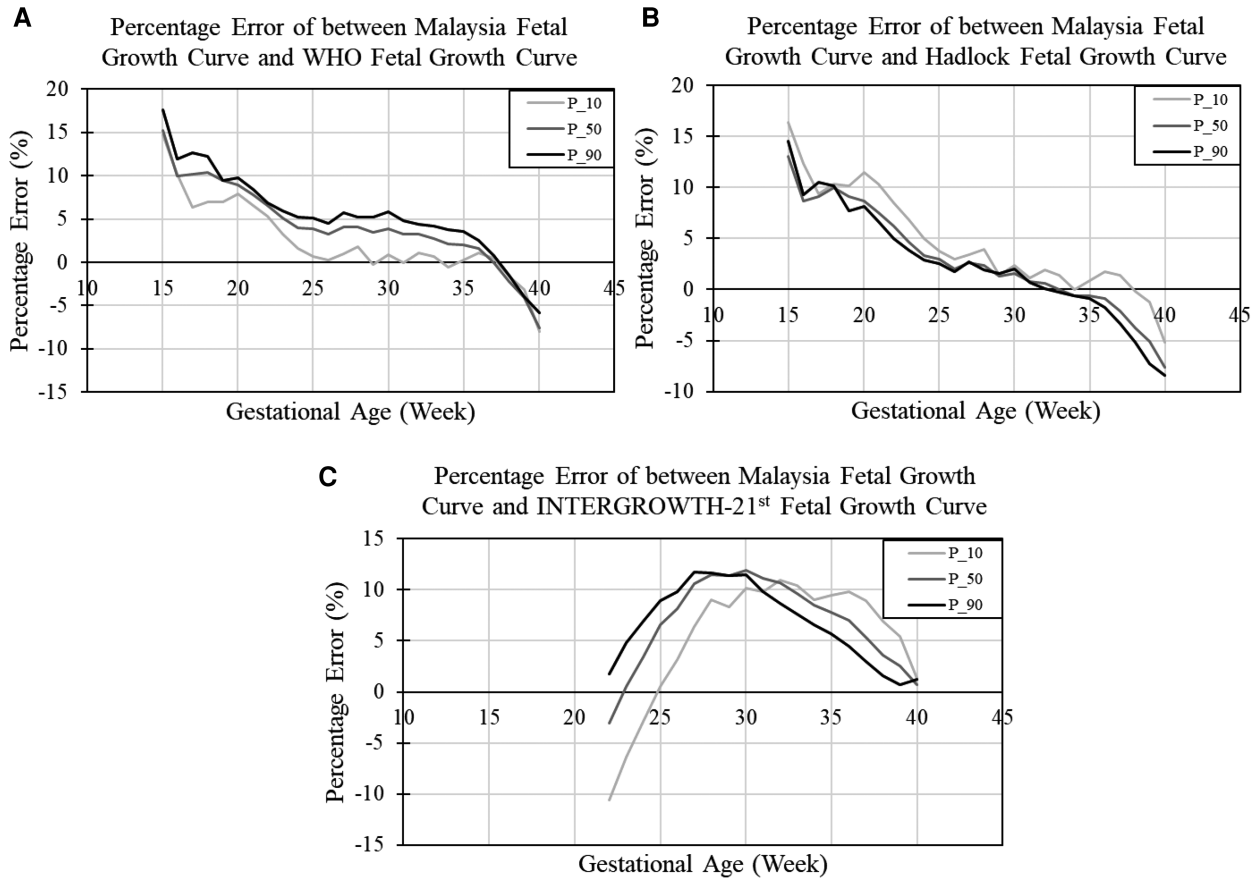

FIGURE 4
Relative percentage difference of estimated fetal weight between Malaysia and (A) WHO, (B) Hadlock, and (C) INTERGROWTH-21st fetal growth curves. *P*_10, *P*_50, and *P*_90 refer to percentage error when comparing the 10th centile, 50th centile, and 90th centile of the two growth charts, respectively.

drop to 59% and Term SGA: 64% drop to 55%). The WHO chart had poor performance in 2nd trimester but improved substantially in 3rd trimester (Balanced Accuracy: Preterm SGA: 66% to 79% and Term SGA: 56% to 67%). The Hadlock chart achieved an average balanced accuracy of 52%–76%.

As compared to the WHO and INTERGROWTH-21st charts, our local growth chart showed a more consistent trend in the 2nd and 3rd trimesters in predicting SGA at birth. The discrepancy of balanced accuracies between the 2nd and 3rd trimesters was as large as compared to the WHO and INTERGROWTH-21st charts. From Table 5 for preterm SGA, our local growth chart achieved 70% balanced accuracy in the 2nd trimester and increased to 78% in the 3rd trimester while for term SGA, our local growth chart shows 58% balanced accuracy in the 2nd trimester and improved to 66% in the 3rd trimester.

TABLE 3 Result of different fetal growth reference charts in predicting SGA at birth.

n = 1,834	Balanced Accuracy	Recall / Sensitivity	Specificity
Hadlock	67%	38%	96%
IG-21st	57%	19%	96%
LMS (Ours)	69%	42%	95%
WHO	69%	43%	96%

n, number of scans; IG-21st, INTERGROWTH-21st.

Discussion

It is known that adopting an international fetal growth chart may not be suitable for certain population. For example, an Italian study and a population-based study in 15 European

TABLE 4 Result of different fetal growth reference charts in predicting SGA for preterm and term infants.

	Type of Growth Charts	Balanced Accuracy	Recall / Sensitivity	Specificity
Preterm (*n* = 228)	Hadlock	74%	59%	90%
	IG-21st	63%	31%	94%
	LMS (Ours)	*76%*	*65%*	*88%*
	WHO	76%	65%	88%
Term (*n* = 1606)	Hadlock	63%	30%	97%
	IG-21st	55%	14%	96%
	LMS (Ours)	*65%*	*34%*	*96%*
	WHO	66%	35%	96%

n: number of scans.

TABLE 5 Result of different fetal growth reference charts in predicting SGA for preterm and term infants in 2nd trimester and 3rd trimester.

	Type of Growth Charts	Balanced Accuracy	Recall / Sensitivity	Specificity
Preterm SGA				
2nd Trimester ($n = 49$)	Hadlock	68%	36%	100%
	IG-21	75%	64%	87%
	LMS (Ours)	***70%***	***45%***	***95%***
	WHO	66%	36%	95%
3rd Trimester ($n = 179$)	Hadlock	76%	65%	87%
	IG-21	59%	23%	96%
	LMS (Ours)	***78%***	***70%***	***86%***
	WHO	79%	72%	86%
Term SGA				
2nd Trimester ($n = 310$)	Hadlock	52%	6%	98%
	IG-21	64%	44%	83%
	LMS (Ours)	***58%***	***22%***	***95%***
	WHO	56%	17%	96%
3rd Trimester ($n = 1296$)	Hadlock	65%	33%	97%
	IG-21	55%	10%	99%
	LMS (Ours)	***66%***	***36%***	***97%***
	WHO	67%	37%	97%

n, number of scans.

countries reported that using international growth charts results in underdiagnosed SGA and FGR fetuses being misclassified as normal growth respectively (9, 10). Furthermore, Asian population from specific areas such South East Asia, are relatively smaller in overall size compared to the white or Caucasian population (7), and thus, adopting an international growth chart in the Malaysian population may misdiagnose SGA or FGR.

Our study's major strength is the inclusion of a very large sample of live births over a span of nine years to construct a national fetal growth chart that can be used as a reference to Malaysia's population. We tested the performance of the local fetal growth chart in predicting SGA at birth using another independent dataset—the 10th-year data. The accuracy of our fetal growth chart in predicting SGA at birth was 69%, depicting similar diagnostic accuracy as the WHO chart, which was constructed with approximately 20% Asian population. Another important point from our study is that our local chart has higher accuracy and sensitivity in predicting preterm SGA at birth in the second trimester would allow possible interventions such as maternal supplementations (26, 27).

The Hadlock growth chart has been widely accepted and used in clinics for fetal growth assessment globally, including in Malaysia. However, we observed that the Hadlock growth chart did not show the best diagnostic accuracy in predicting SGA at birth, achieving only 38% sensitivity and 96% specificity (**Table 3**). When we analyzed the results in the second and third trimesters independently, the sensitivity of the Hadlock growth chart only increased to 49% in the third trimester, which was lower than other studies that reported a sensitivity of 62%–69% (28, 29). The NICHD study reported that the white population had significantly higher fetal growth as compared to the Asian (7), suggesting that adopting a Hadlock growth chart (Caucasian) in our cohort may underdiagnose SGA and hence results in low sensitivity. The same observation was also observed in Papua New Guinea, where the Hadlock chart overestimated the percentage of fetuses with EFW <10th centile (30). This result suggests that adopting the Hadlock chart in Malaysia healthcare institutions may require reconsideration.

Other studies reported that the INTERGROWTH-21st chart did not perform well in identifying SGA at birth (31, 32). For example, a substantial number of fetuses in the Chinese population were being misdiagnosed as at risk of small fetus size (high false positive) (31). In our study, we observed an opposite trend with a significant number of fetuses being misdiagnosis for normal size (high false negative). In fact, the INTERGROWTH-21st chart was the poorest in identifying SGA at birth among all the fetal growth charts. We reckon that the inadequate performance of the INTERGROWTH-21st chart could be due to the discrepancy in the population recruitment criteria where pregnancies with antenatal complications were excluded. The second reason could be EFW is computed using another formula, instead of the Hadlock formula, in the INTERGROWTH-21st study which may result in a discrepancy in EFW estimation (6, 23).

A past study reported that the degree of discrepancy between ultrasound EFW and birth weight increased with the number of days scans completed before delivery (33). This could explain the reason why we observed that all growth charts generally have lower diagnostic accuracy in the second trimester as compared to that in the third trimester, with an 8%–16% decline in performance (**Table 5**). Similar findings were also reported where the sensitivity of predicting SGA at birth in the second trimester was approximately 45% (34, 35). Fetal growth is a dynamic process where it can be affected by various factors such as maternal diet. As such, it is not surprising that the detection rate in the second trimester is poorer than in the third trimester.

Compared with the WHO growth chart, one advantage provided by our local population chart is that it is better at predicting preterm SGA in second trimester (**Table 5**). Preterm SGA is reported to have 13 times higher risk associated with mortality (Kc et al., 2015; García-Basteiro et al., 2017). An earlier recognition of SGA can improve neonatal prognosis and provide an earlier indication of placental disease (36). Detection of SGA in mid-pregnancy could imply that the mothers have a high level of stress, anxiety or depression (37). This information could be helpful to prenatal care planner in designing intervention program in reducing the risk of delivering SGA infant.

One of the study limitations is that we only consider EFW for SGA prediction and did not consider other important covariates, such as maternal variables. However, although customized fetal growth charts have been proposed to improve SGA detection, their predictive ability has been questioned due to methodology bias (38, 39). The second limitation is that the populations selected for this study were urban in Malaysia and thus applying our national growth chart in rural areas may require validation of the performance.

In conclusion, we have constructed five biometric growth charts: biparietal diameter, abdominal circumference, head

circumference, femur length and estimated fetal weight. Our national growth chart achieved 69% accuracy in identifying SGA at birth. The WHO chart better reflects our local population compared to the Hadlock and INTERGROWTH-21st charts. Our population local chart has slightly higher accuracy in predicting preterm SGA in the second trimester which enable prompt identification to implement intervention to increase survival of these infants.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the study protocol by University of Malaya Medical Center, Medical Research Ethical Committee (MREC) with MECID. No: 2021329-9997. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

SNS, AAK, SS, RS and CKL conceived and planned the experiments. All authors provided comments and inputs for designing the experiment. CNL performed data collection. MCL and CNL carried out the data analysis and interpretation of the results. SNS and MCL lead in writing manuscript. All authors discussed the results, provided critical feedback and reviewed the manuscript. SNS supervised the project. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2023.1123948/full#supplementary-material.

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Term breech presentation vaginal births in Tibet: A retrospective analysis of 451 cases

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Background: In high altitude areas, like Tibet, most fetuses in breech presentation at term are delivered vaginally owing to a variety of reasons, but this has not been published.

Objective: This study aimed to provide references and evidence for the delivery of breach presentation term fetuses in high altitude areas, through comparing and analyzing the data of full-term singleton fetuses with breech or cephalic presentation in Naqu People's Hospital, Tibet.

Study design: We retrospectively analyzed the clinical data of 451 breech presentation fetuses mentioned above over a period of 5 years (2016–2020). A total of 526 cephalic presentation fetuses' data within 3 months (1 June to 1 September 2020) of the same period were collected too. Statistics were compared and assembled on fetal mortality, Apgar scores, and severe neonatal complications for both planned cesarean section (CS) and vaginal delivery. In addition, we also analyzed the types of breech presentation, the second stage of labor, and damage to the maternal perineum during vaginal delivery.

Results: Among the 451 cases of breech presentation fetuses, 22 cases (4.9%) elected for CS and 429 cases (95.1%) elected for vaginal delivery. Of the women who chose vaginal trial labor, 17 cases underwent emergency CSs. The perinatal and neonatal mortality rate was 4.2% in the planned vaginal delivery group and the incidence of severe neonatal complications was 11.7% in the transvaginal group, no deaths were detected in the CS group. Among the 526 cephalic control groups with planned vaginal delivery, the perinatal and neonatal mortality was 1.5% ($p=0.012$), and the incidence of severe neonatal complications was 1.9%. Among vaginal breech deliveries, most of them were complete breech presentation (61.17%). Among the 364 cases, the proportion of intact perinea was 45.1%, and first degree lacerations accounted for 40.7%.

Conclusion: In the Tibetan Plateau region, vaginal delivery was less safe than cephalic presentation fetuses for full-term breech presentation fetuses delivered in the lithotomy position. However, if dystocia or fetal distress can be identified in time and then encouraged to convert to cesarean, its safety will be greatly improved.

KEYWORDS

term breech birth, Tibet, neonatal mortality, perineal laceration, stages of labor

1. Introduction

Since the 1970s, the CS rate of fetal breech presentation has risen rapidly (1), in California, United States it rose from 12% in 1970 to 95% in 1999 (2–5). After the Term Breech Trial (6), in some countries including the Netherlands, Sweden, Finland, Norway, and France, a marked increase in the CS rate for term singleton breech presentation fetuses was observed (1, 7). Currently, most of the breech presentations in China undergo CS, with the rate in a hospital in Beijing being as high as 90.68% (8).

However, in Tibet, most breech presentations are still delivered vaginally. The main reasons are as follows: (1) Most of the pregnant women are multipara, and have a high number of births. The progression of their labor is relatively fast as, following the long distance they have usually travelled, by the time they arrive at the hospital the cervical opening is often widely opened; (2) Influenced by traditional beliefs, many pregnant women refuse to have a CS; (3) Some women are concerned that CS may adversely affect a subsequent pregnancy; (4) Tibet is located at a high altitude with consequent lower oxygen levels on the plateau; therefore, fetal weights are lower than in the plain area (an average of 96.98 g lower birth weight for every 1,000 m in elevated maternal altitude) (9, 10), which can make it relatively easier to deliver breech presentations vaginally; (5) Some regions are relatively short of the medical resources needed for CS. Because of the special situation in Tibet, the analysis of our data can reflect the natural state of breech presentation vaginal delivery without intervention. This study aimed to provide a reference and basis for the delivery of full-term breech presentation fetuses in high altitude areas.

In recent years, the neonatal mortality rate in Tibet has dropped significantly, but it still ranks highest in China. A study has shown that the leading causes of neonatal mortality in Tibetan plateau areas include perinatal disease and asphyxia during childbirth (11). Vaginal delivery during breech presentation is undoubtedly one of the risk factors for neonatal complications and death. Therefore, this study creates a guideline for analyzing the causes of neonatal death and reducing the overall mortality rate in Tibet.

2. Materials and methods

From 2016 to 2020, a total of 666 breech presentation fetuses were delivered in our hospital. Excluding non-term fetuses and intrauterine stillbirths, a total of 451 singleton breech presentation fetuses were studied. Of them, 429 had elected a vaginal delivery. The exclusion criteria of breech vaginal delivery were as follows: (i) The umbilical cord was located under the fetal presentation; (ii) fetal growth was restricted (we chose the lowest neonatal birth weight of 2,500 g as the FGR standard); (iii) Suspicious macrosomia (ultrasound estimated fetal weight ≥3,800 g); (iv) Fetal presentation size disproportionate to maternal pelvic size; (v) fetal malformations that obstructed vaginal delivery; (vi) the fetal head was overextended; (vii) the woman refused vaginal trial labor (12, 13). The remaining 22 cases elected a planned CS.

We compared neonatal outcomes of planned CS with planned vaginal delivery, and also compared it with emergency CS following failed vaginal trial labor.

At the same time, a total of 526 cases' clinical data of full-term cephalic fetuses with planned vaginal delivery delivered in Naqu People's Hospital (June 1 and September 1, 2020) were collected as cephalic control group. All cases had elected a vaginal delivery. Neonatal outcomes for cephalic versus breech presentation delivery were analyzed.

The study design is shown in Figure 1.

For each case, experienced obstetricians and pediatricians were present during the vaginal deliveries. The breach fetuses were delivered spontaneously as far as the umbilicus, and the remainder of the body was extracted or delivered with obstetrician's traction and assisted maneuvers, including the Bracht method (14), the Mauriceau Maneuver (15) and etc. All women who delivered vaginally used the classic lithotomy position. No anesthesia was used during labor in the vaginal delivery group. We assessed labor progress by vaginal examination: every 2–4 h in the first stage of labor and every 2 h in the second stage. More frequent examinations could be performed when there was a concern about labor progress (16). Oxytocin was used only when the woman was considered to have secondary atony leading to prolonged labor or fetal distress. The dose of oxytocin was 2.5 U, which was added to 500 ml of glucose and administered by intravenous infusion. Moreover, during vaginal trial labor, the fetal heart rate was monitored throughout using an electronic fetal heart rate monitor. When fetal heart rate monitoring indicated intrauterine hypoxia, the mother was asked to inhale oxygen, she was left in the decubitus position, and was given supplemental nutrition to correct the hypoxia state.

All cephalic vaginal delivery positions also used the classic lithotomy position. Assessment and management of labor were the same as for breech delivery.

The main measures for assessing neonatal outcomes were: perinatal and neonatal mortality (death during childbirth and within 7 days), Apgar score (1 min and 5 min) and severe neonatal morbidity (neonatal encephalopathy, respiratory distress syndrome, intracranial hemorrhage, pneumothorax, joint dislocation, omphalitis, and hyperbilirubinemia).

Neonatal encephalopathy (NE) is a clinically defined syndrome of disturbed neurologic function in the earliest days of life in an infant born at or beyond 35 weeks of gestation, manifested by a subnormal level of consciousness or seizures, and often accompanied by difficulty with initiating and maintaining respiration and depression of tone and reflexes (17). Our diagnosis of NE was mainly based on neuro-psychiatric symptoms and auxiliary examinations such as electroencephalogram (EEG) and MRI.

In addition, we analyzed the duration of the second stage of labor and maternal perineal injuries of breech presentation fetuses by vaginal delivery. The second stage of labor refers to the interval between full cervical dilatation (10 cm) and delivery of the infant; a primipara needed about 3 h and the multipara did not exceed 2 h (18, 19). The classification of perineal lacerations was as follows: (i): Injury to perineal skin only; (ii): injury to the perineum involving perineal muscles but not involving the anal sphincter; (iii): injury to the perineum involving the anal sphincter complex; (iv): injury to the perineum involving the anal sphincter complex (external anal sphincter and internal anal sphincter) and anal epithelium (20).

Different types of breech presentation are described: frank breech and incomplete or complete breech. In a frank breech, the fetus has flexion of both hips, and the legs are straight with the feet near the fetal face. The complete breech has the fetus sitting with flexion of both hips

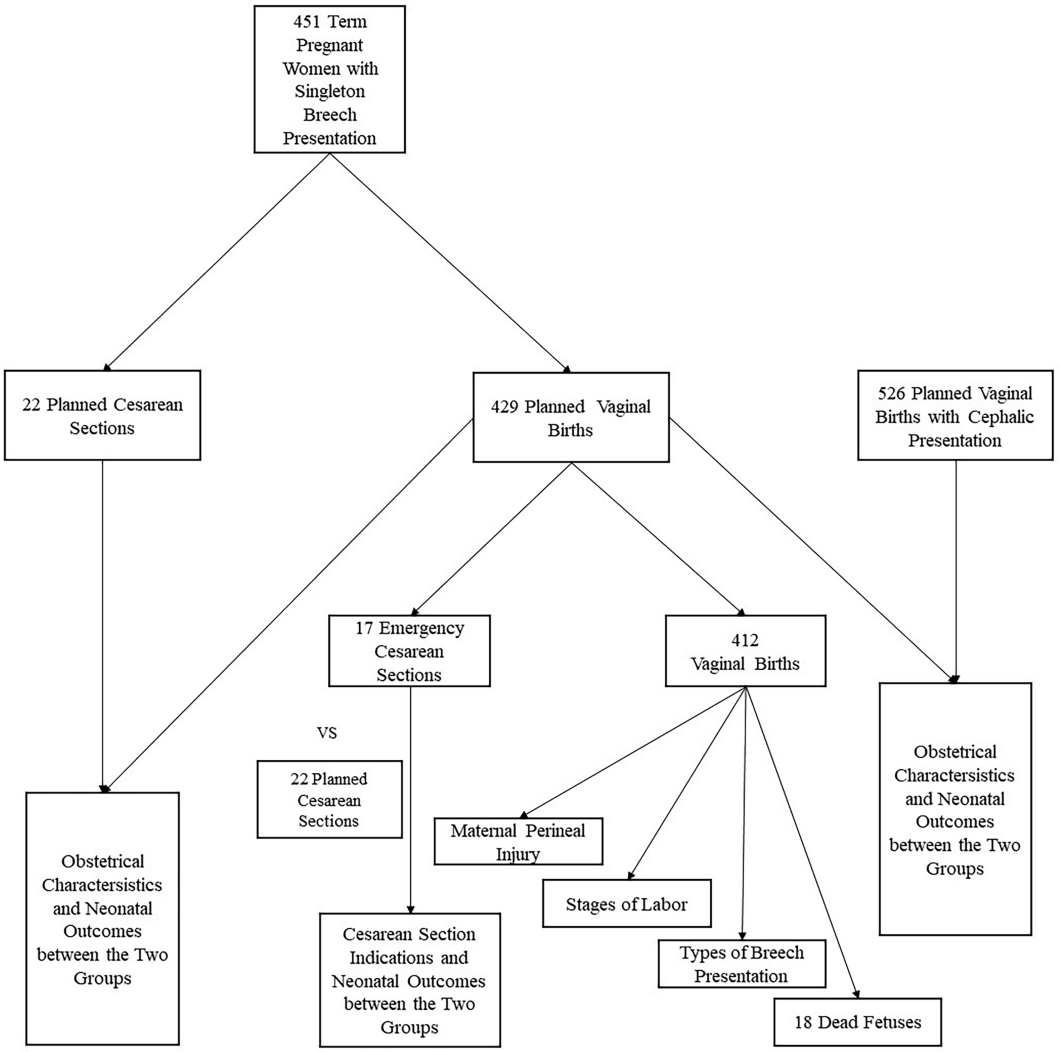

FIGURE 1
Study design. This figure shows the design of the overall study content. We divided 451 full-term singleton breech presentation parturient into planned vaginal delivery group (n=429) and planned cesarean delivery group (n=22), compared the obstetrical characteristics and neonatal outcomes between the two groups. And set a cephalic group, compared indicators mentioned above between cephalic group and breech one. We analyzed the indications for caesarean section in 17 emergency caesarean sections in the group planning for vaginal delivery, and compared the neonatal outcomes between it and the planned cesarean. Maternal perineal injury, stages of labor, types of breech presentation and 18 dead fetuses were analyzed in the vaginal delivery group.

and both legs in a tuck position. Finally, the incomplete breech can have any combination of one or both hips extended (21).

The data were analyzed in this study based on the mode of final delivery. Comparisons were carried out by chi-square test or Fisher's precision test, and the comparison of numbers was t-tested, using $p < 0.05$ to denote statistical significance. Data analysis was performed using SPSS software (26.0).

3. Results

The basic features and neonatal outcomes between planned vaginal delivery versus planned CS of breech presentation fetuses, and between cephalic and breech presentation fetuses with planned vaginal delivery, were analyzed. The basic characteristics of the two comparison groups are shown in Tables 1, 2 and Figures 2, 3. Over the last 5 years, 451 cases of term singleton breech fetuses were delivered in our hospital; among these, 429 (95.1%) had elected for vaginal delivery and 22 (4.9%) had elected for CS. Planned CSs are indicated where the presentation is breech or where the patient refused a vaginal trial. Of women in the elected vaginal delivery group, 17 eventually had an emergency CS due to unsuccessful delivery. The predominant indications for CS were premature rupture of membranes (58.8%), followed by pregnancy-induced hypertension (17.6%), scarred uterus (17.6%), and acute intrauterine fetal distress (5.9%), as shown in Figure 4. Of the 526 cephalic births collected, 24 were converted to emergency CS (4.6%), similar to breech births (4.0%).

Comparisons of the main neonatal outcomes are shown in Tables 3–5. The number of low Apgar scores at 1 min in vaginal delivery infants was significantly higher than that in the CS group, and the difference was statistically significant ($p < 0.01$). However, the difference between the two groups was not statistically significant at

TABLE 1 Characteristics of term breech delivery in the study.

Characteristic	Planned vaginal delivery (n=429, 95.1%)	Planned cesarean delivery (n=22, 4.9%)	95% CI or X^2		p value
Maternal age (years)	28.4 ± 6.8	27.6 ± 6.7	−2.165	3.687	0.610
Nulliparous (No. %)	99 (23.1%)	9 (40.9%)	3.650		0.056
Multiparous (No. %)	330 (76.9%)	13 (59.1%)			
Gestational age (weeks)	39.2 ± 1.41	39.0 ± 1.48	−0.387	0.825	0.478
Birth weight (g)	3,066 ± 418	2,995 ± 243	−43.388	184.434	0.215
Birth weight ≥3,800 g (No.)	20 (4.7%)	0 (0.0%)	Fisher		0.614
Birth weight <2,500 g (No.)	17 (4.0%)	1 (4.5%)	Fisher		0.601

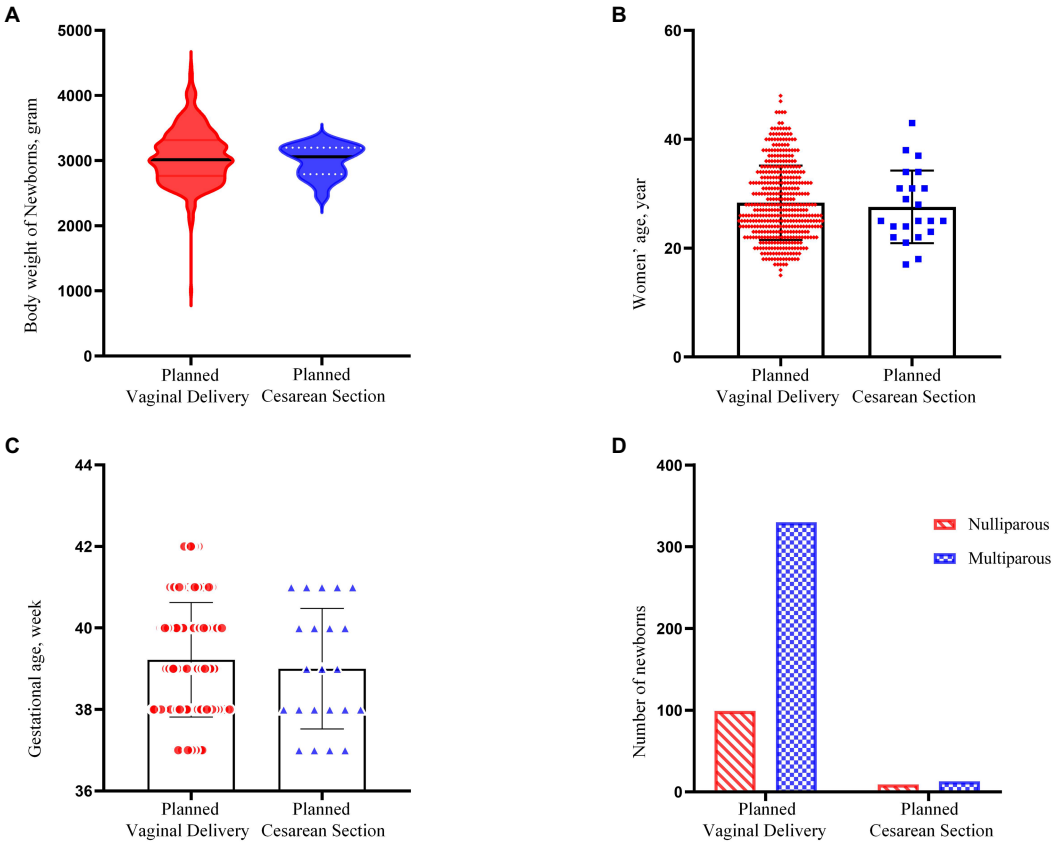

FIGURE 2
Comparison between two modes of breech delivery. **(A–C)** Shows a comparison of body weight of newborns, maternal age and gestational age between the planned vaginal delivery group and the planned cesarean delivery group (p=0.215, 0.610, 0.478, respectively). **(D)** Shows the number of multiparous and nulliparous between two modes of delivery (p=0.056).

5 min (Figure 5). In the cesarean group, there were no deaths or infants with Apgar score <7 at 5 min. Most stillbirths or neonatal deaths were caused by fetal hypoxia during labor, and intrapartum deaths accounted for 61.1% of all deaths. The specifics of the 18 dead fetuses are shown in Table 6. There were no serious neonatal complications in the elected CS group, while the incidence of serious neonatal complications in the elected vaginal delivery group was 4.2%; however, there was no statistical significance between the two groups. In the group planning for vaginal delivery who were transferred to neonatal treatment, 42.3% of them were cured or discharged from hospital; whereas 40.4% of infants requiring treatment were abandoned by their parents because of lack of money.

There was no significant difference in short-term neonatal outcomes between converted CS and elective CS in breech presentation group.

Both the perinatal mortality and severe neonatal morbidity was significantly higher in the breech group than in the cephalic group, and the incidence of neonatal encephalopathy and intracranial hemorrhage was statistically significant. There was a significant difference in the low Apgar score rate between the two groups (breech

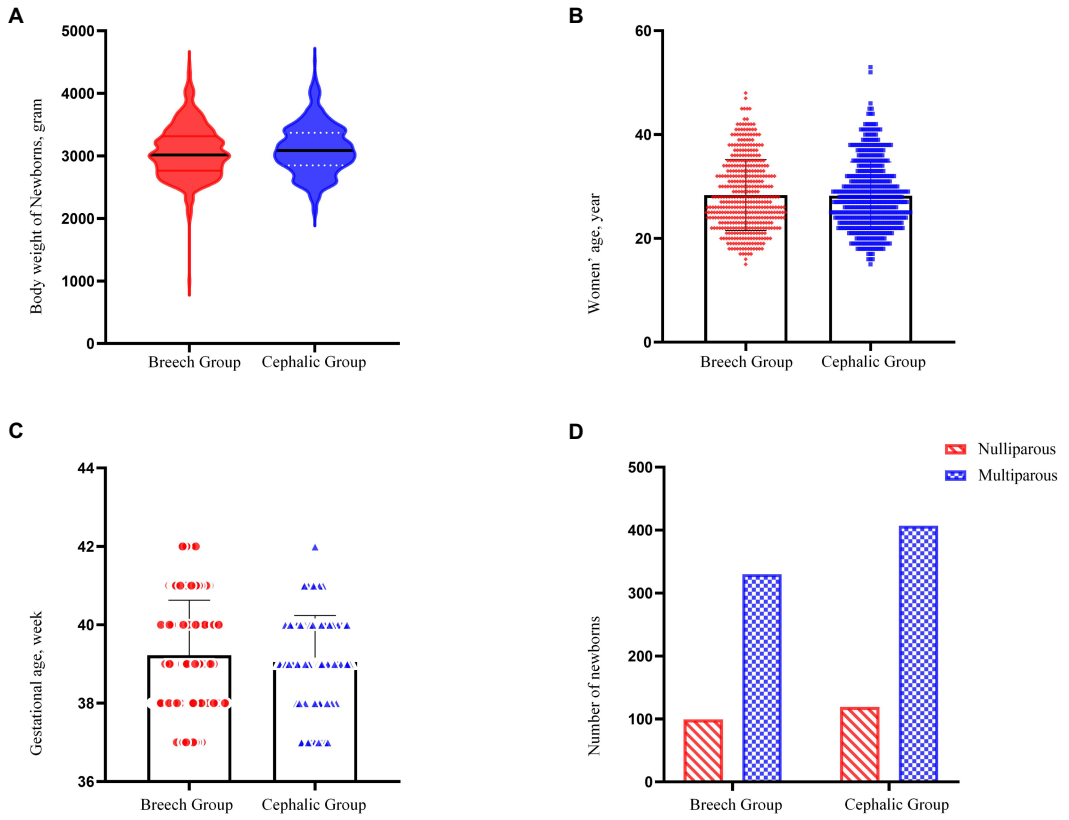

FIGURE 3
Comparison between breech and cephalic presentation. **(A–C)** Shows a comparison of body weight of newborns, maternal age and gestational age between the breech group and cephalic group (p=0.115, 0.761, 0.052, respectively). **(D)** Shows the number of multiparous and nulliparous between two groups (p=0.868).

TABLE 2 Characteristics between term breech and cephalic delivery in the study.

Characteristic	Breech presentation (n=429)	Cephalic presentation (n=526)	95% CI or X^2		p value
Maternal age (years)	28.4 ± 6.8	28.2 ± 6.5	−0.718	0.980	0.761
Nulliparous (No. %)	99 (23.1%)	119 (22.6%)	0.028		0.868
Multiparous (No. %)	330 (76.9%)	407 (77.4%)			
Gestational age (weeks)	39.2 ± 1.4	39.1 ± 1.2	−0.002	0.333	0.052
Birth weight (g)	3,066 ± 418	3,107 ± 397	−93.551	10.205	0.115
Birth weight ≥3,800 g (No.)	20 (4.7%)	24 (4.6%)	0.005		0.942
Birth weight <2,500 g (No.)	17(4.0%)	20(3.8%)	0.016		0.898

group was higher than cephalic group), which was statistically significant at either 1 min or 5 min (Figure 6).

The analysis of the types of breech presentation and maternal perineal damage of fetuses delivered vaginally is shown in Figures 7, 8. Complete breech presentations were the majority (61.2%) of all breech presentations delivered vaginally. Furthermore, among the 364 women we counted, 45.1% of cases had no perineal injury, 1.1% of cases had third degree or fourth degree lacerations, and 8.8% cases had lateral episiotomy.

Data on the second stage of labor is shown in Table 7. For primiparas, the proportion of prolongation of the second stage was 1.2%, while it was 1.6% for multiparas.

4. Discussion

4.1. Principal findings

Our study of deliveries on the Tibetan Plateau found that breech presentation fetuses planning a vaginal birth had a worse short-term prognosis than cephalic fetuses, but there was little difference in rates that converted to cesarean. For term breech presentation fetuses delivered in a typical lithotomy position, the short-term prognosis of CS appears to be better than that of vaginal breech delivery, but there appears to be no difference in short-term neonatal outcomes between elective CS and converting to CS after

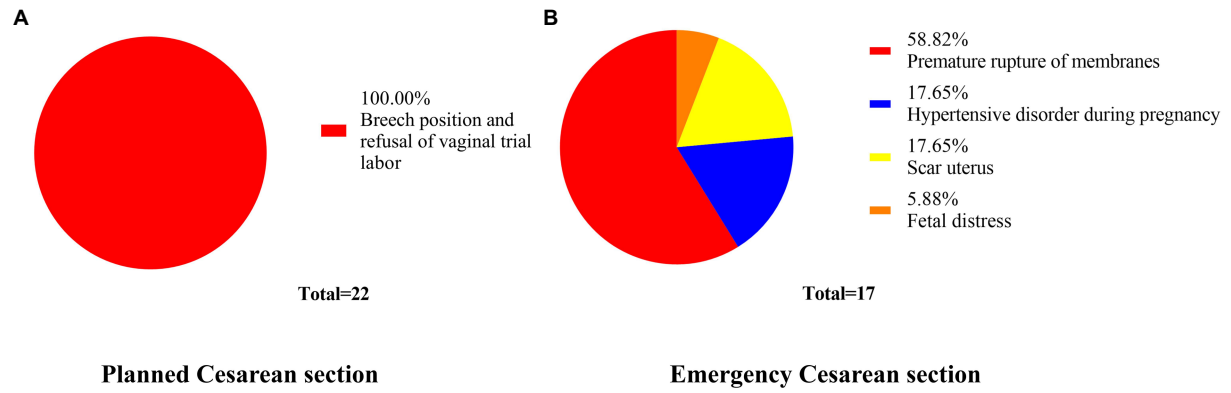

FIGURE 4
Cesarean section indication. All planned cesarean sections were indicated for breech presentation and refusing to undergo vaginal trial labor. Premature rupture of membranes accounts for the largest proportion of emergency caesarean sections. **A** and **B** indicate surgical indications for planned cesarean section versus emergency cesarean section, respectively

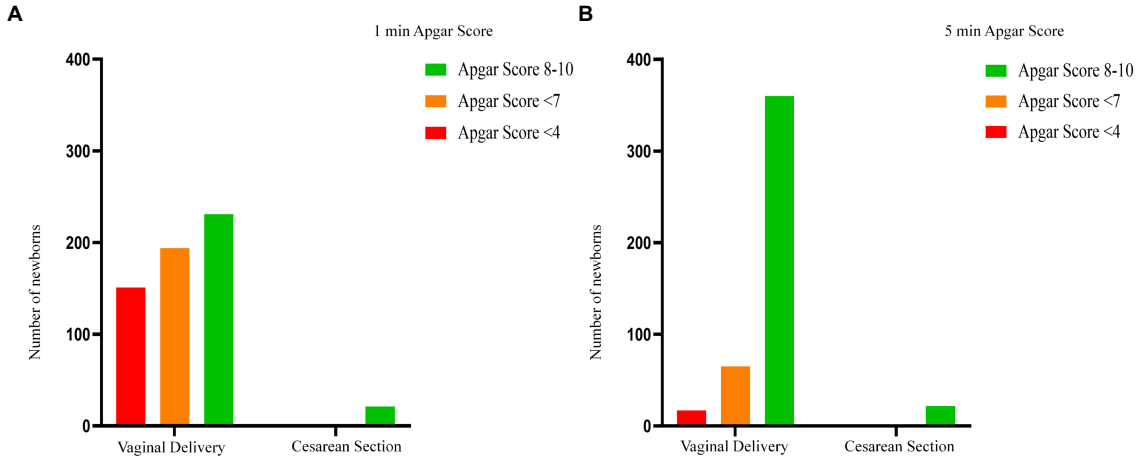

FIGURE 5
Apgar score between two modes of breech delivery. This compared the one-minute and five-minute Apgar score in the planned vaginal delivery group with that in the planned cesarean section group. The number of Apgar scores <7 at 1min in vaginal delivery infants was significantly higher than that in cesarean section group ($p<0.01$). The same difference between the two groups was not statistically significant at 5min ($p=0.096$). In the cesarean section group, there were no infants with Apgar score <7 in 5min. **A** represents the difference in 1-minute Apgar score between the cesarean section group and the vaginal delivery group; and **B** represents the 5-minute Apgar score difference between the two groups.

failed trial delivery. Furthermore, intrapartum death was the leading cause of perinatal death. Improving the operative skills of medical staff, improving medical conditions, timely recognizing dystocia or fetal distress during breech vaginal delivery and encouraging to convert to cesarean is expected to improve the safety of breech vaginal delivery.

4.2. Results

In our cohort of 451 singleton term breech fetuses, perinatal mortality rate in the planned vaginal delivery group with breech presentation was 4.2%, while the cephalic group was just 1.5% ($p=0.012$). Intrapartum deaths accounted for 61.1% of total deaths in breech group. Mortality rates were higher than those reported worldwide by 0.3–1.3% (1, 6) in both cephalic and breech presentation, and the breech group was even higher. This was associated with the limited medical care in the Tibetan plateau area, the poor compliance of pregnant women, the irregularity of obstetric examinations, and the influence of religion and culture. In fact, in Tibet, China, many women lacked awareness of prenatal checkups. Although the government and national health organizations actively disseminated information about pregnancy and have introduced many policies to encourage regular maternity checkups in Tibet, a significant number of pregnant women refused regular prenatal check-ups and failed to detect breech presentation fetuses in time. Their refusal to undergo prenatal check-ups stemmed mainly from their religious beliefs. They believed in their God's guidance and believed that children were God-given treasures, and whether children were healthy or not was God's will and cannot be interfered with. The second reason was that Tibet was sparsely populated, the distance to the hospital was so long, that each prenatal check-up took a long time. And childbirth was a matter that

TABLE 3 Primary outcome of term infants in breech presentation between planned vaginal delivery and cesarean delivery.

	Planned vaginal delivery (*n*=429, 95.1%)	Planned cesarean delivery (*n*=22, 4.9%)	X^2	*p* value
Perinatal or neonatal death	18 (4.2%)	0	Fisher	1.000
Sever neonatal morbidity	50 (11.7%)	0	1.823	0.177
Neonatal encephalopathy	46 (10.7%)	0	1.590	0.208
Intracranial hemorrhage	16 (3.7%)	0	Fisher	1.000
Dislocation of joint	1 (0.2%)	0	Fisher	1.000
Pneumothorax	1 (0.2%)	0	Fisher	1.000
Respiratory distress syndrome	3 (0.7%)	0	Fisher	1.000
Omphalitis	1 (0.2%)	0	Fisher	1.000
Hyperbilirubinemia	5 (1.2%)	0	Fisher	1.000
Apgar score				
<7 at 1 min	194 (45.6%)	1 (4.5%)	14.368	***p* < 0.01**
<4 at 1 min	151 (35.5%)	0	11.804	***p* < 0.01**
<7 at 5 min	65 (15.3%)	0	2.803	0.094
<4 at 5 min	17 (4.0%)	0	Fisher	1.000
Admission to the neonatal care unit	49 (11.4%)	0	1.763	0.184
Pediatric treatment		–	–	–
Healing	22 (42.3%)	0	–	–
Transfer	3 (5.8%)	0	–	–
Death	6 (11.5%)	0	–	–
Give up treatment	21 (40.4%)	0	–	–

"$p < 0.01$" is used to highlight that the value is statistically significant.

local mothers go through many times, so they were not willing to waste time in this.

There were no deaths in either the planned CS group or the emergency CS group for breech vaginal delivery, although the number of CSs in this study was limited, which may have affected the accuracy of the conclusions to some extent, but it was undeniable that in Tibet, under the current medical and cultural background, CS had played a non-negligible role in ensuring the safety of breech delivery.

The number of infants with a low Apgar score at 1 min in the planned vaginal delivery group with breech presentation was significantly higher than that in the CS group, but there was no significant difference at 5 min. Apgar scores are widely used as diagnostic tests for asphyxia (22), and the diagnosis of neonatal asphyxia is based on the 1-min Apgar score. However, numerous studies have shown that delayed Apgar scores are more predictive of severe neonatal incidence than 1-min scores (23–25). A study suggested that full-term infants with an Apgar score below 7 at 5 min were associated with an increased risk of neonatal morbidity, mortality, and neurological deficits (26). Therefore, a low 1-min score may be of limited clinical importance to our study (27). In addition, previous studies show that the 1-min Apgar score in infants delivered vaginally is lower than that in a cesarean delivery group, while the difference in long-term prognosis was not obvious (27–29). This suggests that in our study, the long-term prognosis of newborns in the planned vaginal delivery group may not be worse than in the planned CS group. However, it should not be ignored that the low 1-min Apgar score may be owing to the lack of response to problems encountered during childbirth and neonatal rescue and resuscitation, which to some extent reflects a lack of skills of midwives and neonatologists and the limited medical conditions.

In our study, the incidence of serious neonatal complications was significantly higher in the breech group (11.7%) than in the cephalic group (1.9%) ($p < 0.01$), while the proportion of neonatal complications in the breech group was highest in neonatal encephalopathy. NE may result from acute or chronic hypoxic–ischemic injury, brain malformations, vascular injuries (including stroke), inborn errors of metabolism, and other causes. The diagnosis of Hypoxic–Ischemic Encephalopathy (HIE) was often popular in the United States and other high resource settings, which can be graded as mild, moderate and severe. Due to limited medical resources, we cannot clearly distinguish the etiology of NE in time, but HIE is the main cause of NE (Volpe's study indicated that 50–80% NE cases were considered to have HIE, based on clinical, electroencephalographic (EEG), and MRI criteria) (30), and its prognosis may be different from other neonatal encephalopathies. For example infants with 5 min Apgar score > 7 and NE are unlikely to have long term adverse neurological outcomes due to birth asphyxia (17). Among the 18 deaths in the current study, hypoxic asphyxia was the chief cause, which indicated that hypoxic asphyxia was an important cause of poor neonatal prognosis for fetuses born in breech vaginal delivery in the Tibetan plateau. Breech presentation is an abnormal fetal orientation, and breech vaginal delivery is more likely to cause dystocia and hypoxia than cephalic delivery. However, our study found no significant difference in rates that converted to cesarean between the two groups, and that the breech group had even lower than the cephalic group (4.0% in the breech group versus 4.6% in the cephalic group). It has to be admitted that the lack of medical resources and personnel may be the main reason for this result. Compared to areas with abundant medical resources [29% in some European countries (31)], the rate in Tibet was too low. In fact, at Naqu People's Hospital, every obstetrician was responsible for the delivery of at least 10 women. This was likely to result in a significant proportion of pregnant women with dystocia or fetal distress not being detected in time, resulting in adverse outcomes. This was also illustrated by the low Apgar score rate in the breech group (compared to the cephalic group). The incidence of low scores was significantly higher in the breech group than in the cephalic group, on both one-minute and five-minute scores. This suggested that breech vaginal delivery was a higher risk than in the cephalic delivery.

But is the option of planned vaginal breech not worth supporting? No. Some studies conducted in Finland have shown that neonates delivered vaginally in the breech presentation in high resource settings with hospital specific inclusion criteria and labor management protocols do not have a significant difference in prognosis compared with the head presentation (apart from Apgar suppression), nor does

TABLE 4 Primary outcome of term infants between breech and cephalic presentation.

	Breech presentation (n=429)	Cephalic presentation (n=526)	X^2	p value
Convert to cesarean delivery	17 (4.0%)	24 (4.6%)	0.207	0.649
Perinatal or neonatal death	18 (4.2%)	8 (1.5%)	6.384	**0.012**
Sever neonatal morbidity	50 (11.7%)	10 (1.9%)	38.179	***p* < 0.01**
Neonatal encephalopathy	46 (10.7%)	8 (1.5%)	37.503	***p* < 0.01**
Intracranial hemorrhage	16 (3.7%)	1 (0.2%)	16.931	***p* < 0.01**
Dislocation of joint	1 (0.2%)	0	Fisher	0.449
Pneumothorax	1 (0.2%)	0	Fisher	0.449
Respiratory distress syndrome	3 (0.7%)	1 (0.2%)	0.502	0.479
Omphalitis	1 (0.2%)	0	Fisher	0.449
Hyperbilirubinemia	5 (1.2%)	1 (0.2%)	2.208	0.137
Apgar score				
<7 at 1 min	194 (45.6%)	24 (4.6%)	224.568	***p* < 0.01**
<4 at 1 min	151 (35.5%)	13 (2.5%)	180.006	***p* < 0.01**
<7 at 5 min	65 (15.3%)	12 (2.3%)	53.492	***p* < 0.01**
<4 at 5 min	17 (4.0%)	4 (0.8%)	11.424	***p* < 0.01**

"p <0.01" is used to highlight that the value is statistically significant.

TABLE 5 Primary outcome of term infants in breech presentation between emergency and planned cesarean.

	Emergency cesarean delivery (n=17)	Planned cesarean delivery (n=22)	X^2	p value
Sever neonatal morbidity	1 (5.9%)	0	Fisher	0.436
Neonatal encephalopathy	1 (5.9%)	0	Fisher	0.436
Apgar score				
<7 at 1 min	4 (23.5%)	0	3.495	0.062
<4 at 1 min	1 (5.9%)	0	Fisher	0.436

there be a clear difference in the experience of childbirth (32, 33). This suggests that the safety of breech vaginal delivery remains positive under conditions of rigorous selection and good medical care. In addition, CS has adverse effects on future pregnancies including a rate of uterine rupture in labor of approximately 0.5% in women with one prior cesarean delivery. Uterine rupture may be dramatic with the fetus extruded through the uterine opening requiring urgent cesarean with the potential for considerable maternal and fetal morbidity and mortality. Kenichiro's study indicated that lower maternal educational level was an independent risk factor for uterine rupture among women with prior CS (34). In China, the maternal near miss and stillbirth rates in women with UR were, respectively, 2.35 and 2.12% (35). Due to limited medical resources in Tibet pregnant women often cannot receive timely treatment due to the long journey to seek medical treatment, however with the increase of time (more than 30 min), the adverse neonatal outcomes are increased (36). Ensuring the safety of mothers and babies giving birth in the breech presentation in Tibet requires improving the local medical environment and improving the professional level of medical personnel.

There is literature showing that increasing training for vaginal delivery in the breech presentation of a single fetus can improve the safety of vaginal delivery (37, 38). A study shows that while providing a short-term training program does not change the overall vaginal breech birth rate, it still makes sense for changes in clinical practice, such as the choice of different breech birth positions (39). In addition, a study has proposed that the all-fours position has a better safety profile than classical lithotomy delivery in breech delivery (40). Therefore, improving the professional skills of relevant medical personnel and the medical conditions they work in may be an important part of improving the safety of breach vaginal delivery in Tibet.

Manley's study shows that effective neonatal resuscitation improves neonatal hypoxia and reduces disability in children who survive perinatal asphyxia (41). Oxygen levels in the Tibetan plateau are thinner than in the plains, so improving neonatal resuscitation and rescue techniques is particularly important. This may be an effective way to reduce maternal complications during pregnancy and even maternal mortality in the breech presentation at term during vaginal delivery.

In addition, we found no clear difference in short-term neonatal outcomes for converted CS compared to elective CS. This suggested that timely selection of CS when dystocia or the intrauterine hypoxia can improve the safety of breech vaginal delivery. Wouldn't this be a better option than recommending elective CS for all breech presentation fetuses?

On the other hand, the special religious beliefs in Tibet were also a reason for the low CS rate. Some traditional ideas appear to diverge from modern medical knowledge. Therefore, through strengthening scientific education and popularizing modern medical knowledge in Tibet to balance the influence of traditional Tibetan beliefs with current scientific knowledge regarding birth outcomes is a direction that should be worked towards in the future. The ultimate goal is to promote the lives and health of mothers and children in Tibetan areas.

TABLE 6 Basic information of 18 dead fetuses.

Number	Women's age (year)	Times of birth	Gestational week	Breech presentation	First stage of labor (h)	Second stage of labor (min)	Maternal perineal injury	Birth weight (g)	1 min Apgar score	5 min Apgar score	Transfer to pediatrics	Complication
1	28	4	40	Frank	10	60	I° PL*	4,450	1	4	Yes	NE*, IH*
2	28	3	40	Complete	5	10	I° PL	3,500	1	4	Yes	NE
3	19	3	42	Complete	10.5	80	No injury	3,500	1	3	Yes	AP*, ARDS*
4	45	2	37	Complete	1.5	30	I° PL	2,500	1	2	No	NE
5	20	1	38	Frank	7	20	I° PL	2,900	1	1	No	NE
6	26	3	38	Complete	6	10	No injury	2,900	10	10	Yes	AP*, ARDS*
7	23	1	38	Frank	7	70	PT*	2,600	1	1	No	NE
8	31	6	40	Complete	7	60	No injury	3,510	1	0	No	AX*
9	21	1	40	Frank	5	40	PT	3,500	1	0	No	AX
10	40	3	40	Complete	5	30	PT	3,300	1	0	No	AX
11	32	4	39	Complete	6.83	20	I° PL	3,010	1	0	No	AX
12	18	1	40	Frank	8	80	PT	3,000	1	0	No	AX
13	22	3	38	Complete	8	19	No injury	2,640	1	0	No	AX
14	41	4	37	Complete	6	35	I° PL	2,630	1	0	No	AX
15	41	5	41	Complete	6.5	60	PT	3,500			No	
16	26	2	39	Complete	7	30	No injury	3,000			No	
17	40	4	40	Frank	5	55	No injury	3,000			No	
18	17	1	39	Complete	8	60	III° PL	2,600			No	

*PL is the short form of perineal laceration; PT is the short form of perineotomy; NE is the short form of neonatal encephalopathy; IH is the short form of intracranial hemorrhage; AP is the short form of aspiration pneumonia; ARDS is the short form of acute respiratory distress syndrome; AX is the short form of asphyxia.

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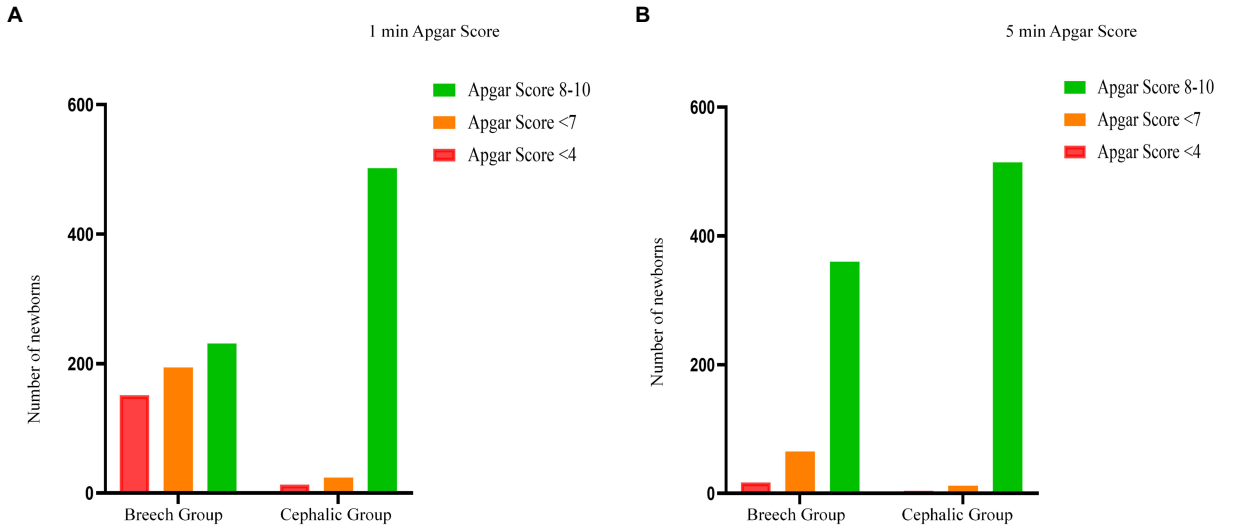

FIGURE 6
Apgar score between breech and cephalic presentation. This compared the one-minute and five-minute Apgar score in the breech group with that in the cephalic group. The number of Apgar scores <7 at 1min and 5min in breech group was significantly higher than that in cephalic group ($p<0.01$, $p<0.01$, respectively). And the number of Apgar scores <4 at 1min and 5min in breech group was also significantly higher ($p<0.01$, $p<0.01$, respectively).

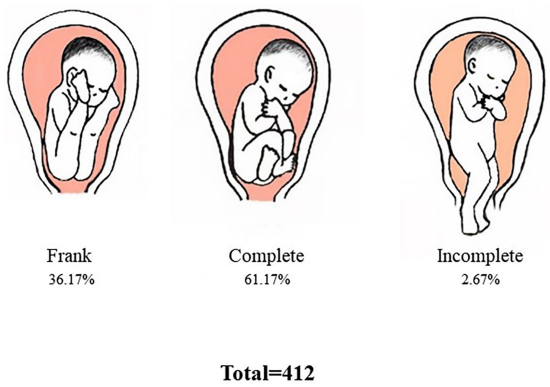

FIGURE 7
Types of breech presentation. This figure shows the type and proportion of the breech position of fetus in the vaginal delivery group. Most of these are complete breech presentation ($n=252$, 61.17%).

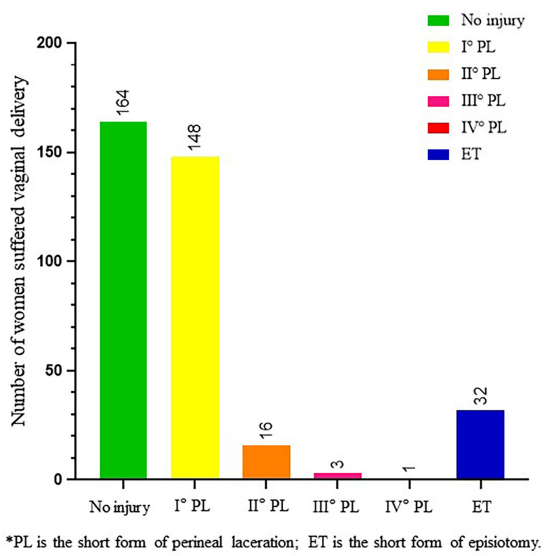

FIGURE 8
Maternal perineal injury. This shows perineal damage during vaginal delivery. Among the 364 women, most women had no perineal injury or had only first degree perineal laceration (45.1, 40.7%, respectively), and severe perineal laceration occurred in only 1.1% of cases.

The average duration of the second stage of labor for both primipara and multipara in our study was longer than the data reported worldwide (40 min for primipara and 14 min for multipara) (42). McKinney JR's study showed that the combined incidence of maternal and neonatal morbidity increases with the duration of the active phase and second stage of labor (43). For full-term fetuses, the second stage of labor with breech presentation is different from that in the cephalic presentation. When the second stage of labor is too long, it may indicate signs of cephalopelvic disproportion and require emergency CS (42). Therefore, obstetricians should pay more attention to the progress of labor, especially the second stage of labor, and appropriately ease the indications of CS to ensure the safety of mothers and infants.

In our study, the rate of third degree or fourth degree perineal laceration and lateral resection was lower than that reported abroad (44, 45). We think these may be associated with low neonatal weight in highland areas and multiple births in pregnant women. However, third degree or fourth degree perineal lacerations can still cause serious problems. It is beneficial to reduce the rate of severe perineal lacerations to improve the safety of vaginally delivered term breech fetuses. There is a study showing that hot compresses and massage can reduce third degree and fourth degree perineal lacerations, and not intervening in advance may reduce the rate of episiotomy (46). CNGOF guidelines recommend that perineal massage during

TABLE 7 Second stage of labor.

	Nulliparous	Multiparous
Mean time (min)	43.1 ± 33.2	35.0 ± 29.9
Prolonged	1 (1.2%)	5 (1.6%)

pregnancy can reduce episiotomy rates and pain in the perineum and anus after childbirth. Furthermore, perineal massage or hot compresses during the second stage of labor can reduce the risk of anal sphincter injury (44).

It has to be mentioned that, owing to poor dependence, even though we had repeatedly emphasized the risk of vaginal breech delivery to patients, they still refused CS; this was also a major factor affecting the risk of maternal and infant outcomes in this study.

4.3. Clinical implications

Due to the high risk of breech presentation delivery, CS has become the optimal delivery method for breech presentation in the economically developed areas of China and even in most countries in the world. Studies on vaginal delivery, especially randomized controlled studies, have become increasingly rare. But the impact of CS on maternal injury and future pregnancies cannot be ignored (for example increased blood loss, infectious morbidity, longer hospitalization, abnormal placentation, risk for thromboembolic phenomenon, risk for uterine rupture and maternal mortality) (47). Due to the unique religious and cultural background and poor medical environment in Tibet, it is particularly important to ensure the health of mothers and children in breech presentation. And with the opening of the three-child policy in China, further research is needed to improve the safety of breech vaginal delivery and strive to provide safer and less damaging options for those pregnant women.

4.4. Research implications

Our study found that in the Tibetan Plateau region, the majority of pregnant women with breech presentation babies still chose vaginal delivery, although the short-term prognosis of CS may be better. However, if it is possible to improve the safety of vaginal delivery of women in special areas such as Tibet by improving medical conditions, improving the skill sets of relevant medical personnel, and timely recognizing dystocia or fetal distress during breech vaginal delivery and encouraging to convert to cesarean, perinatal mortality will be greatly reduced in these areas.

4.5. Strengths and limitations

The strength of this study lay in the fact that its large data base is convincing. And, the study was conducted in the highland area. However, we realize that there are still some limitations to our study. There were low CS rates in our data, which may have contributed to some bias. In addition, all women in our study were delivered in the lithotomy position, lacking relevant controls for delivery in other positions (like a semirecumbent or an all-fours position), it makes the conclusions relatively limited. Our research shows that in the future, we should focus on the training of obstetricians in Tibet on breech delivery techniques and neonatologists on neonatal resuscitation and rescue, strengthening the introduction of obstetricians in Tibet, and strive to improve the safety of breech vaginal delivery.

5. Conclusion

Our study shows that in the Tibetan Plateau region, for singleton term breech presentation fetuses delivered in the lithotomy position, vaginal delivery was less safe than for cephalic presentation fetuses. However, if dystocia or fetal distress can be identified in time and then encouraged to convert to cesarean, its safety will be greatly improved. On the Tibetan Plateau, a relatively large proportion of women choose vaginal delivery, so it is necessary to improve the safety of full-term breech vaginal delivery.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Naqu People's Hospital. Ethics Number: 20200601. Written informed consent was not provided as this is a retrospective study.

Author contributions

ZX developed the idea and design of this study. FL and DG were responsible for collecting, sorting, typing and analyzing data. KY wrote the manuscript. DZ, XX, and ZS critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1048628/full#supplementary-material

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Disrespect and abuse of women during childbirth at health facilities in Eastern Africa: systematic review and meta-analysis

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Background: Disrespectful and abusive maternity care is a sign of poor treatment that influences women's choice to deliver their babies in institutions. Such malpractices continue to go unreported and are rarely exposed in developing countries, despite their serious burden. Therefore, this meta-analysis study aimed to estimate disrespect and abuse of women during childbirth in East Africa.

Methods: PubMed, Google Scholar, Scopus, and Science Direct databases were searched. Data were extracted using Microsoft Excel and analyzed using STATA statistical software (v. 14). Publication bias was checked by forest plot, Begg's rank test, and Egger's regression test. To look for heterogeneity, I^2 was computed, and an overall estimated analysis was carried out. Subgroup analysis was done by study region, sample size, and publication. The pooled odds ratio for associated factors was also computed.

Results: Out of 654 articles assessed, 18 met the criteria and were included in this study. There were a total of 12,434 study participants. The pooled prevalence of disrespect and abuse of women during childbirth in East Africa was 46.85% (95% CI: 45.26.72–66.98), I^2 = 81.9%. It was lower in studies with sample size greater than 5000 (33%). The disrespect and abuse rates between community-based studies (44.96%) and institutional-based studies (47.35%) did not differ significantly, though. Instrumental delivery (AOR = 2.70; 95%CI: 1.79–4.08), presence of complications (AOR = 6.41; 95% CI: 1.36–30.14), receiving care at government hospitals (AOR = 3.66; 95% CI: 1.09–12.23), and poor wealth index (AOR = 2.16; 95% CI: 1.26–3.70) were associated factors.

Conclusion: In East Africa, disrespect and abuse of women during childbirth was high. Instrumental delivery, presence of complications during childbirth, receiving

care at government hospitals and poor wealth index were predictors of maternal disrespect and abuse. Safe delivery practice should be promoted. Training in compassionate and respectful maternity care, particularly in public hospitals, has also been recommended.

KEYWORDS

disrespect, abuse, mistreatment, childbirth, meta-analysis, East Africa

Introduction

Maternal mortality and morbidity among women of reproductive age in poor nations are primarily caused by complications during pregnancy and childbirth (1). There is widespread agreement that professional birthing services provided within a formal healthcare system can reduce the risk of maternal fatalities (2). More than 162,000 women still lose their lives in pregnancy and childbirth each year in sub-Saharan Africa (SSA). Most such fatalities occur within a day of delivery (3).

The East African countries are Burundi, Ethiopia, Comoros, Uganda, Rwanda, Tanzania, Mozambique, Madagascar, Zimbabwe, Kenya, and Zambia are among the poorest in the world and have low access to and affordability of maternal healthcare services (4). Moreover, the risk of adverse effects on the mother and the child is increased by a lack of access to appropriate obstetric care, particularly during delivery. Due to this service gap, women end up having poor maternal outcomes. In East Africa, the risk of death for those mothers is 1 in 31, compared to 1 in 4,300 in a high-income country (5).

A woman's rights during maternity care are violated by disrespect and abuse (D&A), which is also referred to as mistreatment, obstetric violence, or dehumanized care (6). Women's human rights are violated when they are treated disrespectfully and violently while receiving facility-based maternity care. This also keeps women from using maternal health services, erodes their satisfaction and confidence in the healthcare system, and results in unfavorable pregnancy outcomes (7–10). Respectful maternal care during facility-based maternity care is recommended by the World Health Organization (WHO) as a fundamental method for improving the quality of maternity services, to decrease disrespect and abuse as well as maternal mortality and morbidity (11). The biggest obstacle to receiving quality maternity care globally, however, is the growing evidence of the disrespect, abuse, and mistreatment of women throughout labor, delivery, and the postpartum period (10, 12, 13).

Growing data demonstrates that disrespect and abuse of maternal care, to varied degrees and severity, happens globally (14). Additionally, this research demonstrates that women get disrespectful and harsh care during childbirth (14). To ensure physical safety during institutional delivery, the quality of maternal health services is constrained (15, 16). Many women, however, do not receive the medically and culturally appropriate treatment that they require (17).

According to the Universal Declaration of the Rights of the Childbearing Woman, every woman has the right to sexual and reproductive healthcare that is respectful and dignified, including during childbirth (18, 19). As a result, abuse during childbirth may constitute a violation of women's fundamental human rights (20) and may act as a strong deterrent to women seeking care in facilities for subsequent pregnancies (21–23). A seven-category model was proposed by Bowser and Hill in a landscape analysis of the evidence for disrespect and abuse in facility-based childbirth that was published (24). This model was intended to generate discussion and a research agenda for implementation, not to provide a thorough analysis of the available evidence. Physical abuse, non-consented clinical care, non-confidential care, substandard care, discrimination, abandonment, and imprisonment in health facilities (23) have all been major themes in more recent research on this subject (25–28).

Stress, exhaustion, irritation, and a lack of job satisfaction all have an impact on a healthcare provider's negative behavior. The working environment and conditions at the facility, as well as work-related issues like severe workloads, long working hours, lax supervision, strained relationships with coworkers, and inadequate pay, all have an impact on these problems (7, 24, 29). Disrespect and abusive at these facilities has reportedly been linked to women's underuse of healthcare facilities during birthing (23, 30, 31).

Several negative effects of D&A on women's health and wellbeing have been documented, including fear about using medical facilities (24), an increased chance of birth complications (32), low self-ratings of health, sleeping issues, and symptoms of post-traumatic stress disorder (33). The prevalence of disrespect and abuse ranged from 15% in Tanzania (28) to 98% in Nigeria (27).

There are no data at the country level, despite the fact that numerous primary researches have confirmed disrespect and abuse during child birth in East Africa. Therefore, the goal of this systematic review and meta-analysis study was to determine the prevalence of disrespect and abuse of women during childbirth in East Africa and its determinants. Clinicians and other stakeholders will be able to address gaps in disrespect and abuse of women during childbirth and operational plans based on the study's findings, which will provide them with the fundamental knowledge they need to provide every child bearing women.

Methods

Data synthesis and reporting

We conducted data analysis based on a single measurement result (disrespect and abuse). Tables, text, and a forest plot

are used to present the results. Using the standard PRISMA checklist guideline, this systematic review and meta-analysis study was carried out to assess the overall prevalence of disrespect and abuse of women during child birth in East Africa (34) (**Supplementary Table 1**).

Search strategy

Articles on the disrespect and abuse in East Africa were searched using international online databases (Pub Med, Science Direct, Scopus, EMBASE, and Google Scholar). The following keywords and search terms were used during the search: "prevalence," "disrespect," "abuse," "delivery," "obstetric," "parturition," "maternity care," "mistreatment during pregnancy," "attitude of health personnel," "professional misconduct," and "East Africa." Boolean operators like "OR" and "AND" were used to combine the search phrases as well as use them separately. The Population Exposure Controls and Outcome (PECO) searching guidelines were used to perform the search strategy and retrieve relevant articles from the databases specified above. The search was carried out from October 1, 2022, until November 1, 2022.

Study outcome

Any act of physical abuse, non-confidential care, non-consented care, non-dignified care, abandonment of care, discrimination, or detention in the facilities during childbirth is considered disrespectful and abusive behavior (35).

Inclusion and exclusion criteria

The papers that were included in this meta-analysis were those that were conducted in East African nations, were published in English, and had full texts that could be searched. Studies that included data on the disrespect and abuse of child birth were also reported on. Qualitative studies, studies from developed countries, research from duplicated sources, and articles missing the complete text were all omitted from this systematic review and meta-analysis. The eligibility of the included articles in this study was determined using the COCOPOP (Condition, Context, and Population) paradigm. Laboring women made up the study population (POP), with the prevalence of disrespect and abuse serving as the condition (CO), and only studies carried out in East-Africa serving as the context (CO).

Quality assessment

Two authors (NG and KT) independently assessed the standard of the research using the Joanna Briggs Institute (JBI) standardized quality appraisal checklist (36). The disagreement raised during the quality assessment was resolved through a discussion led by the third author (GA). The critical analysis checklist has eight parameters with yes, no, unclear, and not applicable options. The parameters involve the following questions:

(1) Where were the criteria for inclusion in the sample clearly defined?
(2) Were the study subjects and, therefore, the setting described in detail?
(3) Was the exposure measured result validly and reliably?
(4) Were the main objective and standard criteria used to measure the event?
(5) Were confounding factors identified?
(6) Were strategies to affect confounding factors stated?
(7) Were the results measured indeed and dependably? And (8) Was the statistical analysis suitable? Studies were considered low risk when they scored 50% and above on the quality assessment indicators, as reported in a **supplementary file** (**Supplementary Table 2**).

Risk of bias assessment

Through the Hoy et al. (37) established bias assessment tool, which consists of 10 items that assess four domains of bias as well as internal and external validity, two writers (NG and GA) independently evaluated included papers for risk of bias. Any disagreement raised during the risk of bias assessment was resolved through a discussion led by the third author (KT). Finally, the argument was solved and reached with an agreement. The first four questions (items 1–4) assess whether there is selection bias, non–response bias, and external validity. The last six questions (items 5–10) evaluate the presence of measurement bias, analysis-related bias, and internal validity. Studies were labeled as having a "low risk of bias" if they answered "yes" to eight or more of the ten questions. Studies classed as "moderate risk" if they answered "yes" to six to seven of the ten questions, whereas studies classified as "high risk" if they answered "yes" to five or fewer of the ten questions, according to information in a **supplementary file** (**Supplementary Table 3**).

Data extraction

Data extraction and analysis were carried out using STATA 14 software and a Microsoft Excel spreadsheet from 2016, respectively. Using a standardized Joanna Briggs Institute data extraction format, two authors (NG and KT) separately extracted all pertinent data. The disagreement raised during data extraction was resolved through a discussion led by the third author (GA). Finally, the argument was solved and reached with an agreement. Due to this study's lack of a paper form, the data automation tool was not employed (manual data). The first author's name, the year of publication, the study region, the study setting, the study design, the sample size, the prevalence of the prevalence of disrespect and abuse, the unadjusted odd ratio for variables, and the quality of each paper were retrieved.

Data analysis

The data were exported to STATA software version 14 for analysis after being extracted from all pertinent findings

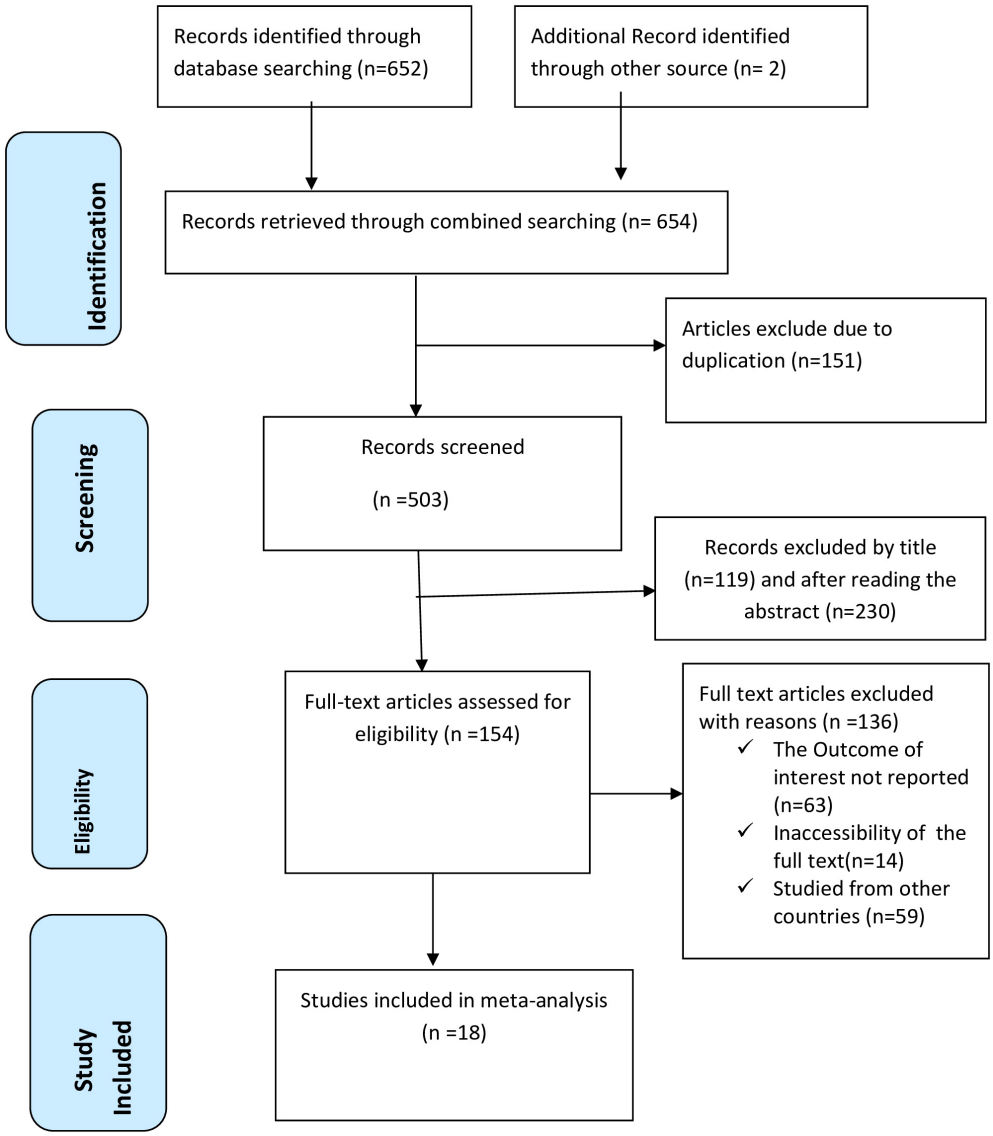

FIGURE 1
PRISMA flow chart displays the article selection process for the prevalence of disrespect and abuse of women during childbirth in East Africa.

in a Microsoft Excel spreadsheet. A weighted inverse variance random-effects model was used in a meta-analysis to produce a pooled OR. The presence of heterogeneity was visually evaluated using a forest plot, which was then utilized to analyze and estimate the pooled estimate of disrespect and abuse. Analysis of subgroups was done based on the study setting and sample size. Sensitivity analysis was used to determine the impact of a single study on the meta-analysis estimate of prevalence as a whole. The funnel plot was used to examine potential publication bias, and Begg and Egger's regression tests were used to examine it more objectively. The trim-and-fill method proposed by Duval and Tweedie (38) was used to control publication bias. Cochran's Q X^2 test and I^2 statistics were used to test for heterogeneity, estimate the amount of total/residual heterogeneity, and measure variability caused by heterogeneity, respectively (39). A Univar ate meta-regression analysis was used to examine the effects of sample size and publication year variations on between-study heterogeneity (40).

Results

Search results and study characteristics

We retrieved a total of 654 articles from various international online databases, such as PubMed, Scopus, EMBASE, Science Direct, and Google Scholar. After excluding duplicate research, we were left with 503 studies that were chosen for full title and abstract screening. The remaining 154 studies were screened for full text articles after 349 studies were eliminated because of the titles and abstracts. After reviewing the full text, 136 articles were excluded for further reasons. Finally, this systematic review and meta-analysis study's inclusion criteria included 18 articles (26, 28, 35, 41–56) with 12,434 study participants (**Figure 1**).

Each of the included studies yielded low risk results and used a cross-sectional study methodology. The remaining studies were community-based, while 14 were cross-sectional

TABLE 1 Characteristics of studies included in the systematic review and meta-analysis of disrespect and abuse of women during childbirth in East Africa.

References	Country	Setting	Design	Sample size	Mean age	Prevalence	Response rate	Quality
Mihret et al. (41)	Ethiopia	Institutional	Cross-sectional	369	NR	15.9%	98.6%	Low-risk
Phillipo (42)	Tanzania	Institutional	Cross-sectional	263	NR	31.2%	100%	Low-risk
Samdo et al. (12)	Tanzania	Institutional	Cross-sectional	1914	25	15%	NR	Low-risk
Altahir et al. (51)	South Sudan	Institutional	Cross-sectional	2109	28	77.2%%	100%	Low-risk
Siraji et al. (43)	Ethiopia	Institutional	Cross-sectional	290	NR	91.7%	100%	Low-risk
Mengistie Zeleke and Melkie Bayeh (44)	Ethiopia	Institutional	Cross-sectional	407	29.11	49.6%	97.1%	Low-risk
Mekonnen et al. (45)	Ethiopia	Institutional	Cross-sectional	565	25.2	37.5%	97.4%	Low-risk
Kruk et al. (26)	Tanzania	Community	Cross-sectional	1779	25.86	19.48%	70.6%	Low-risk
Maldie et al. (46)	Ethiopia	Institutional	Cross-sectional	374	30.05	79.4%	98.7%	Low-risk
Gebremichael et al. (47)	Ethiopia	Community	Cross-sectional	1124	26.8	22%	100%	Low-risk
Banks et al. (48)	Ethiopia	Institutional	Cross-sectional	204	NR	21.1%	100%	Low-risk
Makumi et al. (49)	Kenya	Community	Cross-sectional	207	NR	71.9%	87.3%	Low-risk
Wassihun et al. (50)	Ethiopia	Community	Cross-sectional	422	28.6	67.1%	97.2%	Low-risk
Ukke et al. (52)	Ethiopia	Institutional	Cross-sectional	281	28.5	98.9%	100%	Low-risk
Kebede et al. (53)	Ethiopia	Institutional	Cross-sectional	409	31.3	52.1%	100%	Low-risk
Tagesse et al. (54)	Ethiopia	Institutional	Cross-sectional	557	26.8	46.9	95%	Low-risk
Negash et al. (55)	Ethiopia	Institutional	Cross-sectional	548	26	46.9%	95%	Low-risk
Tekle Bobo et al. (56)	Ethiopia	Institutional	Cross-sectional	612	NR	74.8%	100	Low-risk

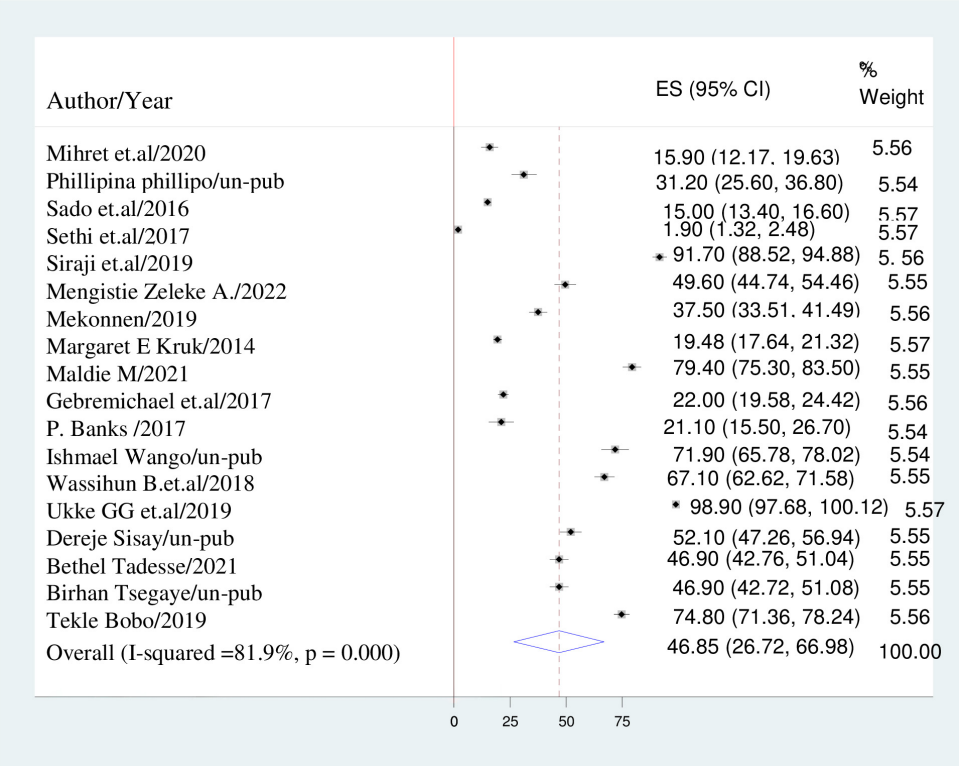

FIGURE 2
Forest plot displaying the pooled prevalence of disrespect and abuse of women during childbirth in East-Africa.

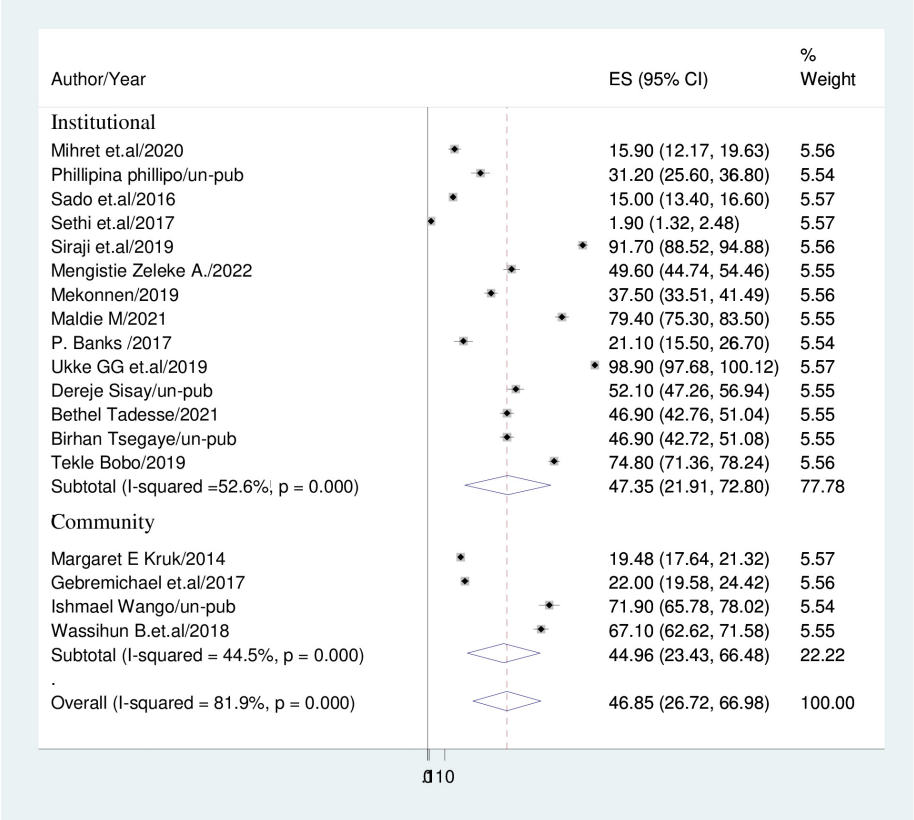

FIGURE 3
Forest plot displaying sub-group analysis based on study setting.

studies carried out at healthcare facilities. Thirteen studies were carried out in Ethiopia (41, 43–48, 50–56), three in Tanzania (26, 28, 42), one in Kenya (49), and one in Sudan (51). Sample sizes varied from 204 to 2109. Disrespect and abuse of women during childbirth varied in prevalence from 1.9 to 98.9% (Table 1).

Meta-analysis

Prevalence of disrespect and abuse during childbirth

The overall estimate of disrespect and abuse during childbirth was computed using a DerSimonian and Laird random-effects model. As a result, the heterogeneity index (I^2) was 81.9% ($p < 0.001$) and the pooled prevalence of disrespect and abuse of women during childbirth among women in East Africa was 46.85% (95% CI: 26.72, 66.97) (Figure 2).

Subgroup analysis

Subgroup analysis based on sample size and study setting was carried out because this meta-analysis revealed a notable heterogeneity. Because of this, community based studies had the lower prevalence of disrespect and abuse during childbirth (44.96%; 95% CI: 23.43, 66.48); I^2 = 44.5% than institutional based studies (47.35%; 95% CI: 21.91, 72.80); I^2 = 52.6% (Figure 3). Studies with sample sizes of less than 500 had a prevalence of disrespect and abuse of women (57.92%; 95% CI: 36.83, 79.01); I^2 = 29.3% while studies with sample sizes of more than 500 had a prevalence of (33%; 95% CI: 18.54, 47.44); I^2 = 19.8% (Figure 4).

Heterogeneity and publication bias

We calculated a sub-group analysis based on sample size, and study setting to correct the reported heterogeneity of this study (I^2 = 81.9%). Additionally, a univariate meta-regression utilizing the sample size and year as covariates was conducted to determine the root cause of heterogeneity. It demonstrated that the variability between research was unaffected by sample size or the year (Table 2).

A funnel plot was used to analyze the presence of publication bias visually, while the Egger's test and Begg's test were used to assess it objectively. The funnel plot shows an unequal distribution of studies upon visual observation (Figure 5). The Egger test (p = 0.002) and Begg test (p = 0.041) suggested a significant publication bias, thus we conducted Duval and Tweedie trim-and-fill analysis to address it across the studies. The pooled prevalence of disrespect and abuse of women during facility childbirth was revised to 1.7% after the inclusion of eight studies within the fill and trim analysis. Therefore, trim fill analysis was employed to correct

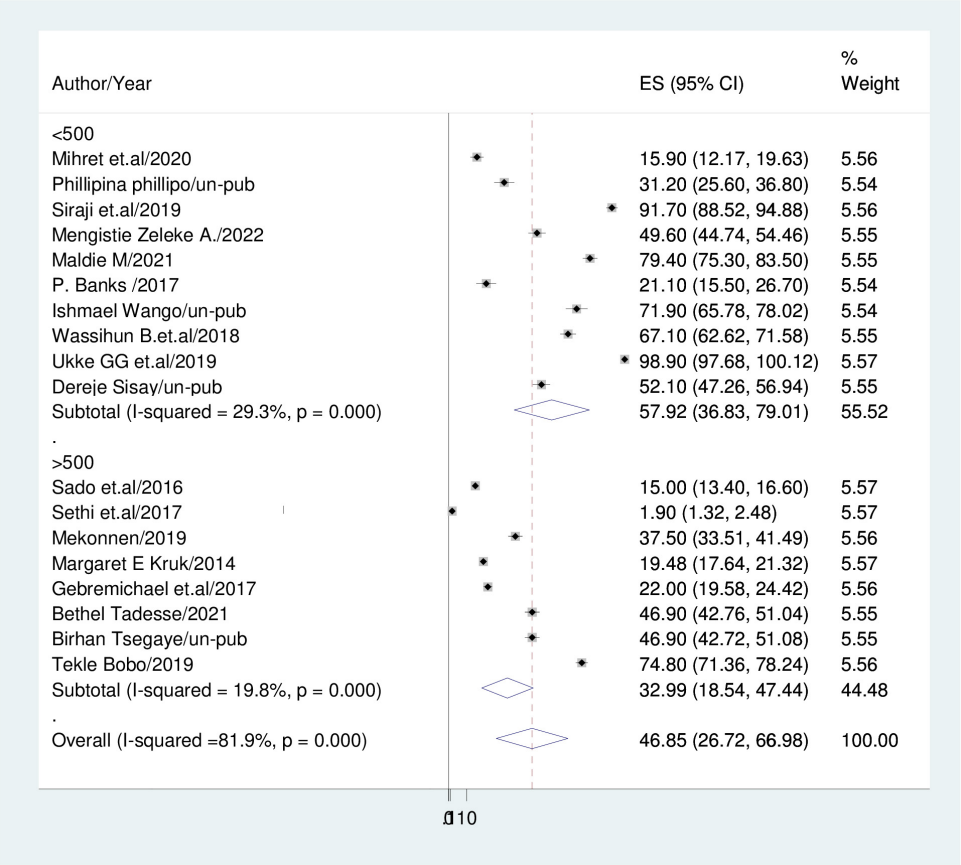

FIGURE 4
Forest plot displaying subgroup-analysis based on sample size.

publication bias when eight papers were included in the funnel plot (Figure 6).

We also did a counter-enhanced funnel plot to identify potential causes of the funnel plot's asymmetry. Given that the majority of this area contains regions with statistically significance, publication bias is more likely to be the main cause of this funnel asymmetry ($P < 0.01$). Different shaded patches are present to show statistical significance. In particular, p-values higher than 0.10 correspond to the center white shaded area, p-values between 0.10 and 0.05 to the heavy gray shaded region, p-values between 0.05 and 0.01 to the medium gray shaded region, and p-values less than 0.01 to the area outside the funnel (Figure 7).

Leave −one-out-sensitivity analysis

A leave-one-out sensitivity analysis was carried out to detect the effect of each study on the overall prevalence of disrespect and abuse of women during childbirth by excluding one study at a time. In the sensitivity analysis, both Altahir et al. and Ukke et al. showed an impact on the pooled prevalence of disrespect and abuse of women during childbirth at health facility (Table 3).

TABLE 2 Meta-regression analysis of factors affecting between-study heterogeneity.

Heterogeneity source	Coefficient's	Standard error	p-value
Sample size	4.29	3.07	0.21
Year	−63.74	68.41	0.95

Factors associated with disrespect and abuse during childbirth

In this study, presence of complication during childbirth, receiving care at government hospitals, instrumental delivery, and poor wealth index were candidate variables of disrespect and abuse. Therefore, maternal disrespect and abuse were significantly associated with the presence of complications during childbirth, instrumental delivery, receiving of care at public hospitals and poor wealth index.

Instrumental delivery

According to this study, women who gave birth with instrumental delivery were 2.7 times more likely to be disrespected and abused as compared to women who gave birth with spontaneous vaginal delivery (stocktickerAOR = 2.70; 95%CI: 1.79,4.08). Random effect model was applied because

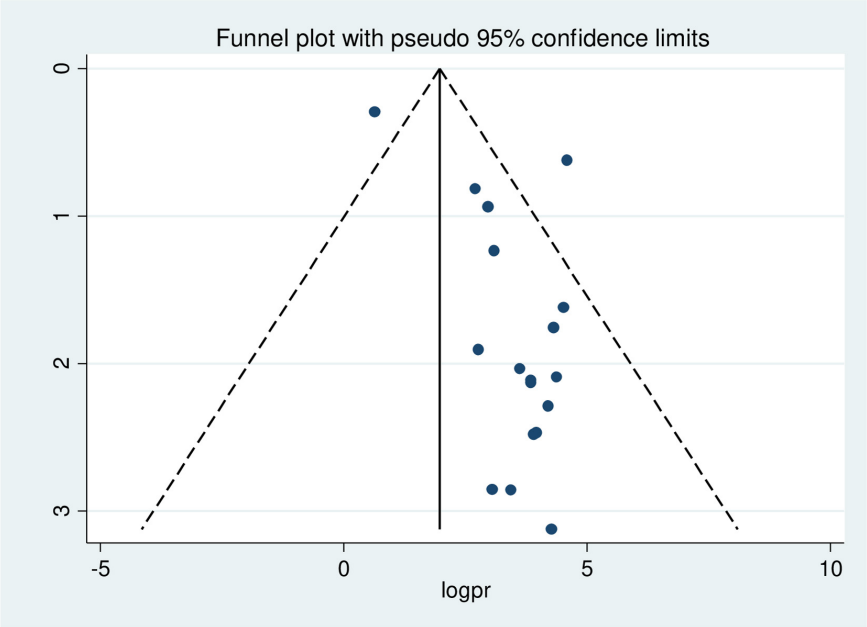

FIGURE 5
Funnel plot showing asymmetrical distribution of studies indicating the presence of publication bias.

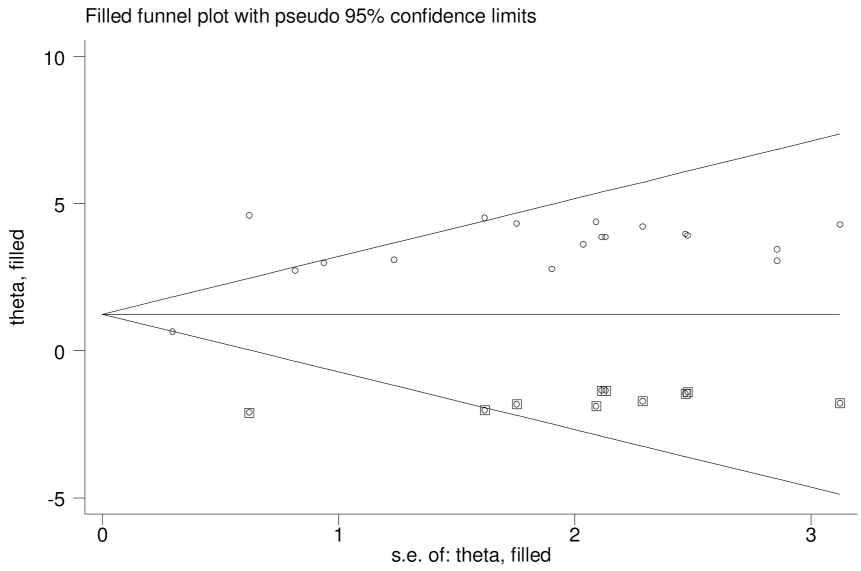

FIGURE 6
Trim and fill methods of analysis displaying the presence of eight missing studies causing for funnel plot asymmetry.

of the existence of heterogeneity between studies (I^2 = 57.3%) (Figure 8).

Presence of complication during childbirth

This meta-analysis found that women who had complications during childbirth were six times more likely to be disrespected and abused than women who didn't have complication during childbirth (AOR = 6.41%;95%CI: 1.36–30.14). A random effect model was assumed because the value of I^2 was 71.6% (Figure 9).

Receiving of care at government hospitals

In this study, the odds of maternal disrespect and abuse during childbirth in government hospitals were 3.6 times higher than

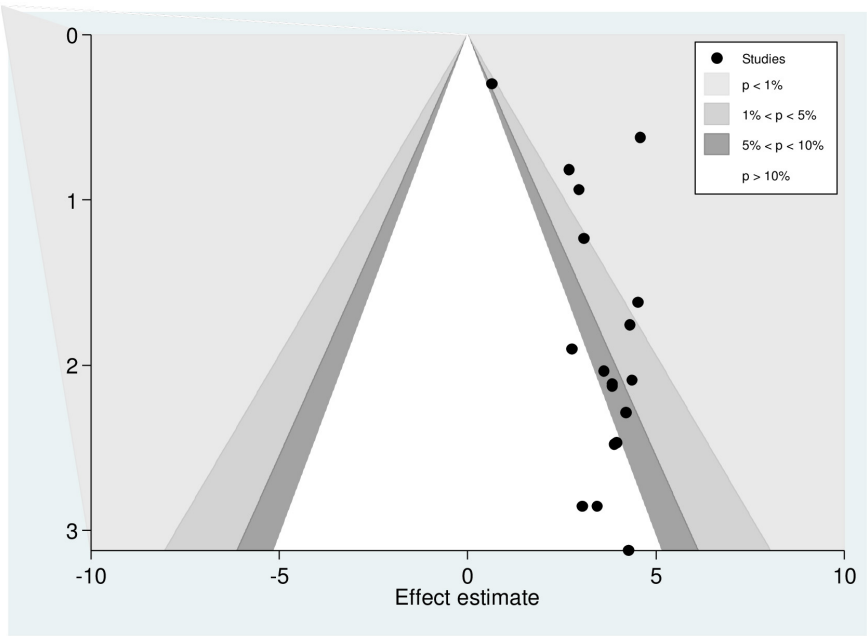

FIGURE 7
Counter-enhanced funnel plot showing that funnel plot asymmetry is due to the presence of publication bias.

their counterparts (AOR = 3.66; 95%CI: 1.09–12.23). Because of I^2 static indicated heterogeneity (89.6%), a random effect model was selected for the analysis (Figure 10).

TABLE 3 The pooled prevalence of disrespect and abuse of women during childbirth in East Africa when one study omitted from the analysis a step at a time.

Study omitted	Estimate	95% CI
Mihret et al. (41)	48.67	27.67–69.67
Phillipo (42)	47.77	26.93–68.61
Sando et al. (12)	48.73	26.33–71.12
Altahir et al. (51)	49.50	30.98–68.01
Siraji et al. (43)	44.21	23.84–64.57
Mengistie Zeleke and Melkie Bayeh (44)	46.69	25.84–67.53
Mekonnen et al. (45)	47.40	26.44–68.36
Kruk et al. (26)	48.46	26.47–70.46
Maldie et al. (46)	44.93	24.27–65.60
Gebremichael et al. (47)	48.31	26.87–69.75
Banks et al. (48)	48.36	27.52–69.20
Makumi et al. (49)	45.38	24.66–66.10
Wassihun et al. (50)	45.66	24.89–66.43
Ukke et al. (52)	43.77	29.95–57.58
Kebede et al. (53)	46.54	25.71–67.38
Tagesse et al. (54)	46.85	25.94–67.75
Negash et al. (55)	46.85	25.94–67.75
Tekle Bobo et al. (56)	45.20	24.50–65.91
Combined	46.85	26.72–66.98

Poor wealth index

The chance of maternal disrespect and abuse of women who had poor wealth index were two times higher than women who had rich wealth index (AOR = 2.16; 95%CI: 1.26–3.70). We utilized random effect model because of the presence of heterogeneity (I^2 = 46.2%) (Figure 11).

Discussion

The fundamental rights of women, newborns, and families are violated when women are treated disrespectfully or violently when giving birth at a medical facility. One of the world's biggest problems is the mistreatment of women who are giving birth in medical facilities. Due to the focus on reducing both maternal and newborn morbidity and mortality through the implementation of various measures such boosting institutional delivery and woman-friendly care. Meanwhile, using institutional delivery is difficult because of the disrespect and mistreatment of women while they are giving birth in a medical facility.

Three areas are highlighted in the World Health Organization's (WHO) vision for the quality of maternal and newborn health under the experience component of quality of care: communication, emotional support, and dignity and respect (57). Dignity and respect place a premium on providing care that upholds women's rights to privacy, confidentiality, and freedom from mistreatment such physical and verbal abuse and discrimination (58). In poor nations where a big proportion of clients are served by a small number of care professionals, disrespect and abuse are frequently more of an issue (58).

To improve the standard of care and the use of expert delivery services, respectful care during labor must be promoted (59). Abuse and disrespect have a negative impact on the use

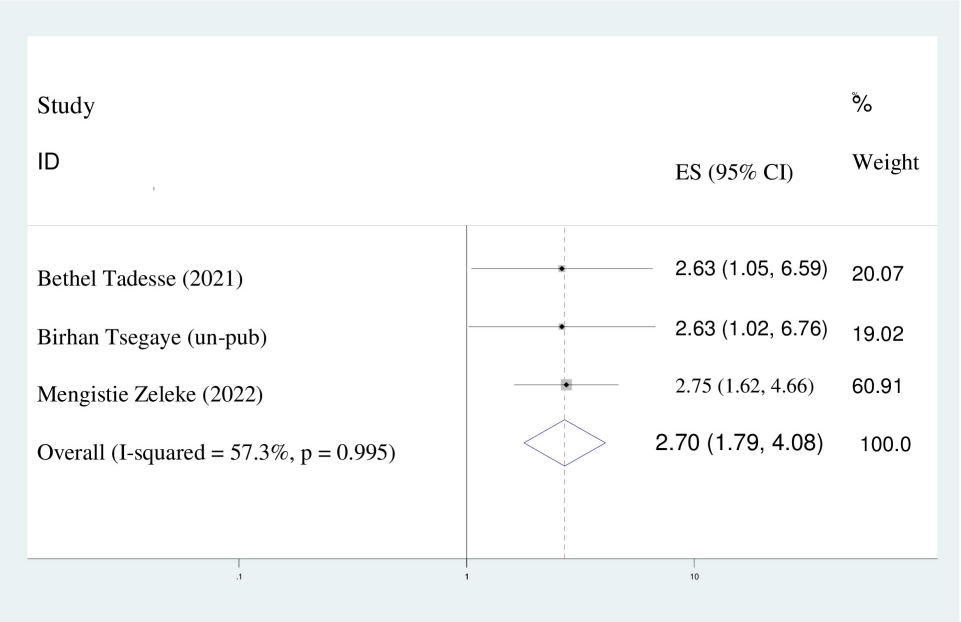

FIGURE 8
The pooled odds ratio displaying the association of instrumental delivery with disrespect and abuse of women.

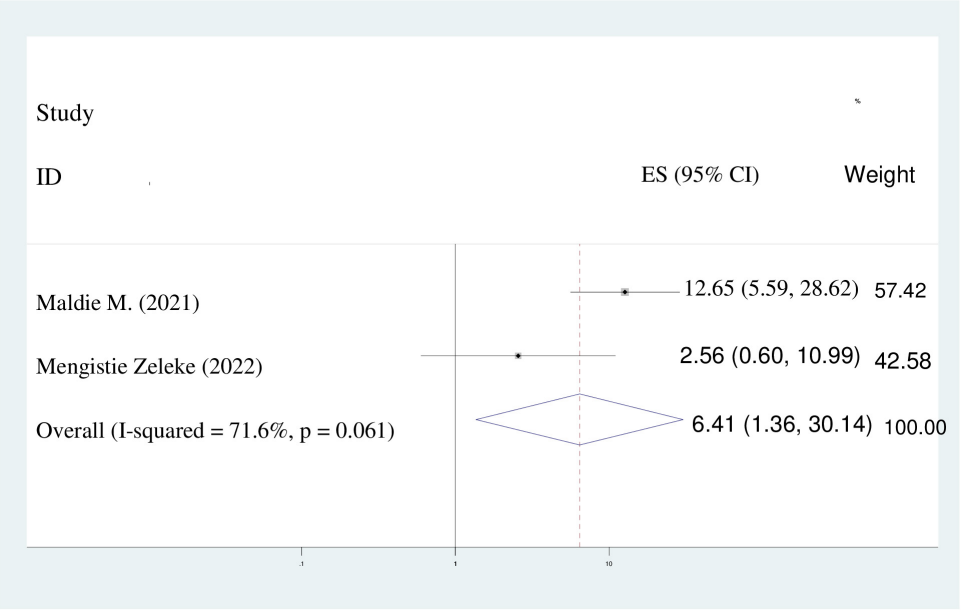

FIGURE 9
Pooled odds ratio displaying the association of presence of complications during childbirth with disrespect and abuse.

of competent delivery services, an intervention that has been shown to significantly lower maternal mortality across the globe (60). The key findings were that the estimate of disrespect and abuse of women during childbirth and disrespect and abuse of women were significantly related to the maternal wealth status, receiving at governmental hospitals, presence of complication during childbirth and instrumental delivery. The purpose of this systematic review and meta-analyses was to ascertain the general prevalence of disrespect and abuse among East African women as well as the factors that contribute to it. Therefore, the overall prevalence of disrespect and abuse of women during childbirth was 46.85% (95% CI: 26.72–66.98) in this study. The results of the current study are in line with meta-analysis studies conducted in Ethiopia (49.4%) (36) and Sub-Saharan African nations (44.09%) (61). This could be as a result of the research locations' shared socioeconomic traits.

The results of this study are lower than those from studies done in Nepal (70.1%) (62), India (60%, 84.3%) (63, 64), Iran (75.5%)

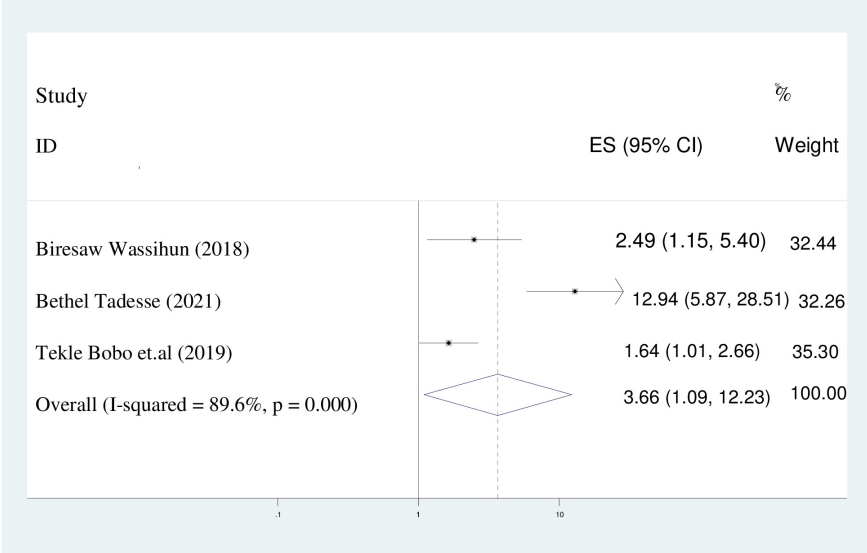

FIGURE 10
Pooled odds ratio displaying the association of receiving care at government hospitals with disrespect and abuse of women.

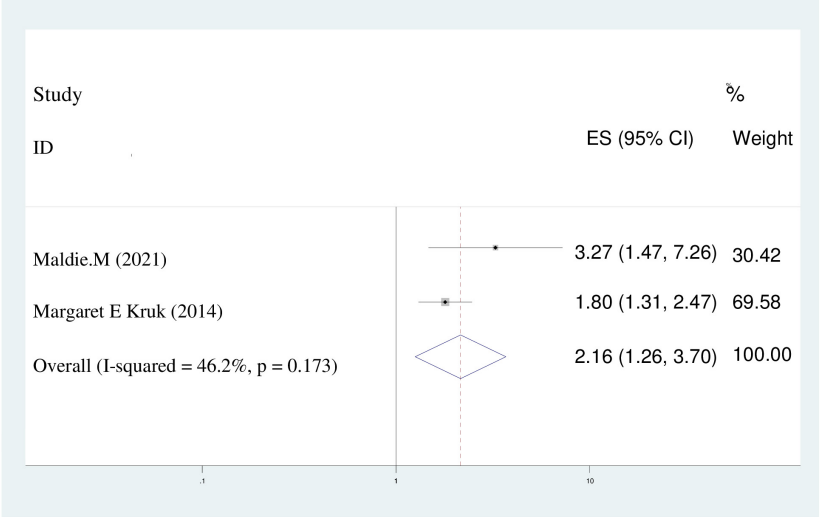

FIGURE 11
Pooled odds ratio displaying the association of poor wealth index with disrespect and abuse of women.

(65), Pakistan 97.4% (66), Pakistan 99.7% (67), and Peru 97.4% (68). The study population, the different health facility set up, and the definition of disrespect and abuse all may have an impact.

The results of this study was higher than those of studies conducted in Mexico (18.8%) (69), Brazil (18.3%) (70) and India (28%) (71) in comparison. Socioeconomic differences, variations in healthcare providers' knowledge, attitudes, and skills, variations in healthcare facilities and systems, variations in study time and sampling methods, and differences in how disrespect and abuse of women during childbirth are defined at various healthcare facilities could all be contributing factors.

In thesis meta-analysis, presence of complication during childbirth, receiving care at governmental hospitals, poor wealth index, and instrumental delivery were predictors of maternal disrespect and abuse during childbirth. Women who utilized an instrument had a 2.7 higher likelihood of being disrespected and abused than those who gave delivery naturally vaginally. Studies from Pakistan (66) and India (64, 72) and their findings are in agreement with this one. The greater patient load and unfavorable patient-provider ratio in medical facilities may be the cause. The current study's findings may be explained by the fact that, in comparison to higher-level settings, the delivery of health services in low-level settings is hampered by a lack of standards, leadership, supervision, and quality clinical care, as well as by a severe lack of multidisciplinary teams and training.

There was a 6-fold increase in the likelihood of disrespect and maltreatment among women who experienced complications during labor. This result agrees with the findings of the Indian study

(72). She may have become susceptible to disrespect and abuse because of the risk of labor complications, which might have put the midwives on edge. Alternatively, the abuse or perceived disrespect may have been an effort by the midwives to shift the burden for the complications to her. There may be a statistically significant correlation between the lack of access to high-quality maternity care and disrespect and abuse of women. This is a crucial discovery since maternal stress of any kind slows down the labor process and raises the risk of problems (73). Therefore, in order to enhance maternal health outcomes, it is necessary to address the types of abusive provider behavior that can lead to difficulties.

According to this study, women with low wealth indices were twice as likely to experience abuse and contempt as women with high wealth indices. This result is in line with research conducted in Pakistan (74). The explanation could be because facility-based healthcare personnel treat wealthier women with greater respect and consideration than impoverished ones.

In contrast to women receiving care at private hospitals, the current study found that women receiving care at public hospitals were 3.7 times more likely to experience abuse and contempt.

The possible explanation for this is that, in contrast to health centers where there may be relatively fewer complicated cases and care providers are less stretched, hospitals with higher case loads and overflowing referrals of complicated cases that cause overcrowding may push care providers to provide abusive care.

In this study, a random-effect model was utilized to address a sizable variance that occurred in between-study heterogeneity. No single study significantly influenced the overall prevalence of disrespect and abuse of women, according to the results of a leave-one-out sensitivity analysis. To determine the presence of heterogeneity, sub-group analysis based on sample size, and study settings was conducted. The considerable heterogeneity may result from variations in the sample populations, variations in the paper's properties, or variations in socio-cultural factor.

Conclusion

To sum up, there was a significant frequency of abuse and disrespect toward women in East Africa after childbirth. The prevalence of disrespect and abuse of women during childbirth also varied depending on the study location and sample size. Significantly contributing factors to disrespect and abuse of women during childbirth included the presence of maternal difficulties during childbirth, low wealth index, receiving care at a government hospital, and instrumental delivery. It is advised that medical professionals adhere to the concepts of compassionate and respectful maternity care. Additionally, spontaneous vaginal birth and safe delivery practices have been recommended.

Strength and limitations

This study has some limitations. First, the study protocol was not registered in the prospective international register of systematic reviews (PROSPERO). Second, articles were restricted to only being published in the English language. Third, all of the included studies were cross-sectional, which might affect the outcome variable because of other confounding factors.

This research has some strength. First, compressive electronic online international searching engines were used. Second, the predictors of disrespect and abuse were discovered.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

NG conceptualized the study. NG and GA contributed to during data extraction and analysis. NG and KT wrote result interpretation. NG, GA, and KT prepared the first draft, contributed during the conceptualization and interpretation of results and substantial revision, and revised and finalized the final draft manuscript. All the authors read and approved the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1117116/full#supplementary-material

SUPPLEMENTARY TABLE 1
Prisma checklist.

SUPPLEMENTARY TABLE 2
Methodological quality assessment of included studies using Joanna Brigg's Institute quality appraisal criteria scale (JBI). The eight item questions assessing inclusion criteria, study setting and participant, exposure measurement, objectives, confounder, statically analysis, outcome measurement and dealing confounder were used.

SUPPLEMENTARY TABLE 3
Risk of bias assessment for the included studies. The ten item questions of which four items assess external and six items assess internal validity were used.

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Improved neonatal outcomes by multidisciplinary simulation—a contemporary practice in the demonstration area of China

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Background: Simulation-based training improves neonatal resuscitation and decreases perinatal mortality in low- and middle-income countries. Interdisciplinary in-situ simulation may promote quality care in neonatal resuscitation. However, there is limited information regarding the effect of multidisciplinary in-situ simulation training (MIST) on neonatal outcomes. We aimed to investigate the impact of MIST on neonatal resuscitation in reducing the incidence of neonatal asphyxia and related morbidities.

Methods: Weekly MIST on neonatal resuscitation has been conducted through neonatal and obstetrical collaboration at the University of Hong Kong-Shenzhen Hospital, China, since 2019. Each simulation was facilitated by two instructors and performed by three health care providers from obstetric and neonatal intensive care units, followed by a debriefing of the participants and several designated observers. The incidence of neonatal asphyxia, severe asphyxia, hypoxic-ischemic encephalopathy (HIE), and meconium aspiration syndrome (MAS) before (2017–2018) and after (2019–2020) the commencement of weekly MIST were analyzed.

Results: There were 81 simulation cases including the resuscitation of preterm neonates of different gestational ages, perinatal distress, meconium-stained amniotic fluid, and congenital heart disease with 1,503 participant counts (225 active participants). The respective incidence of neonatal asphyxia, severe asphyxia, HIE, and MAS decreased significantly after MIST (0.64%, 0.06%, 0.01%, and 0.09% vs. 0.84%, 0.14%, 0.10%, and 0.19%, respectively, all $P < 0.05$).

Conclusions: Weekly MIST on neonatal resuscitation decreased the incidence of neonatal asphyxia, severe asphyxia, HIE, and MAS. Implementation of regular resuscitation simulation training is feasible and may improve the quality of neonatal resuscitation with better neonatal outcomes in low- and middle-income countries.

KEYWORDS

neonatal resuscitation, in-situ simulation training, multidisciplinary, neonatal outcomes, asphyxia

Abbreviations

CC, chest compression; HBB, Helping Babies Breathe; HCPs, health care providers; HIE, hypoxic-ischemic encephalopathy; ILCOR, International resuscitation Liaison Committee; MAS, meconium aspiration syndrome; MR SOPA ventilation corrective steps, Mask adjustment, Reposition of the airway, Suction the mouth and nose, Opening mouth, increasing Pressure and placing Alternative airway; MSAF, meconium-stained amniotic fluid; Neonatal Intensive Care Unit, NICU; NRP®, Neonatal Resuscitation Program®; PPV, positive pressure ventilation; SP, standardized patient.

1. Introduction

Most neonatal deaths, which contribute to almost half of the deaths of children under 5 years old, occur in low- and middle-income countries and regions, with preterm birth complications and intrapartum-related events (previously called birth asphyxia) as the most common causes (1). Neonatal resuscitation has the potential to prevent perinatal deaths of nearly 2 million infants due to asphyxia every year (2). Effective and prompt resuscitation in the delivery room could improve neonatal outcomes (3–7). However, the basic skills of neonatal resuscitation in the delivery room and compliance with guidelines are insufficient (8, 9).

Many studies support the efficacy of neonatal resuscitation training in improving knowledge and performance (10), through the translation of the science of resuscitation into a training program. Neonatal resuscitation training resulted in significant improvement in clinical outcomes, with decreased neonatal and perinatal mortality in low- and middle-income countries (10–13). After the Neonatal Resuscitation Program (NRP®) training was implemented in China, the incidence of neonatal asphyxia in respective regions declined from 6.32% in 2003 to 2.94% in 2008, and the mortality rate declined from 7.55 to 3.41 per 10,000 livebirths (14).

While resuscitation training was found to improve immediate knowledge and skill acquisition, one-time training may not be sufficient for sustained knowledge, or the incorporation of key skills related to resuscitation into clinical practice (15). In addition to that, improved performance in the simulation environment may not be transferable to the clinical setting (16). Skills decline more than knowledge over time (17, 18) and structured practice and refresher training could maintain neonatal resuscitation skills (18, 19). In 2015, the ILCOR pointed out that the increase in training frequency could improve providers' self-confidence and recommended that the training frequency should be more than once a year (20). However, evidence remains inconclusive on the maintenance of resuscitation skills, the optimal interval of repeated training, and conversion to clinical performance. As defined by the Society for Simulation in Healthcare in the Healthcare Simulation Dictionary (second edition), in-situ simulation is the training taking place in the actual patient care setting/environment in an effort to achieve a high level of fidelity and realism (21). In-situ simulation-based training can foster and maintain newborn ventilation skills in a multidisciplinary delivery unit staff in a high-resource setting (22). Multidisciplinary in-situ simulation training (MIST) may effectively improve technical skills and teamwork in neonatal resuscitation. However, the impact of real-life neonatal resuscitation is unknown (23).

We describe our 2-year practice of collaborative MIST on neonatal resuscitation and concomitant neonatal outcomes. The goal of MIST on neonatal resuscitation was primarily to strengthen behavioral skills, and secondarily to reinforce technical skills and the adherence to NRP® algorithm through simulation and subsequent debriefing. We aimed to evaluate the impact of MIST conducted through neonatal and obstetrical collaboration on the incidence of neonatal asphyxia and related complications. The feasibility and barriers to developing MIST on neonatal resuscitation were also investigated and discussed. We tested the hypothesis that frequent and regular MIST on neonatal resuscitation would improve acute neonatal outcomes.

2. Methods

This study was approved by the Institutional Review Board of the University of Hong Kong-Shenzhen Hospital (HKU-SZH), China. Shenzhen is a relatively high-income region in an area known as the Demonstration Area of China, representing a developed area in a developing country where innovative practices can be tried and implemented. The HKU-SZH has approximately 6,000–8,000 deliveries annually and a neonatal intensive care unit (NICU) with 40 level-III and level-II beds. The NICU has an average admission of 350 high-risk neonates per year. Since its opening in 2012, HKU-SZH has introduced evidence-based neonatal resuscitation workshops to provide training to NICU staff and midwives. The curriculum is based on ILCOR guidelines and NRP® with modifications for the context in China (24). In HKU-SZH, all neonatologists, NICU physicians and nurses, midwives, and obstetricians have to satisfactorily complete a 2-day neonatal resuscitation workshop and successful recertification every 2 years.

Since 2019, MIST on neonatal resuscitation has been conducted through neonatal and obstetrical collaboration regularly every Wednesday morning in a delivery room. After completion of training in neonatal resuscitation, all providers would participate in the weekly MIST. The simulation was facilitated by 2 instructors, participated by 3 providers from the obstetric unit and NICU, followed by debriefing which was observed by several designated observers (**Figure 1**). The set-up of the resuscitation cart, which is used for simulation only, is the same as that for clinical use. The instructors were certified locally by experienced Canadian and American NRP® certified instructors through HKU-SZH Train-the-Trainer programs after they completed an instructor training course in China, as currently there is no mutual agreement between the American Academy of Pediatrics and the China Medical Association on NRP® training.

The **Supplementary Material** shows the different phases of the MIST and the roles of instructors, providers, and designated observers.

2.1. Different Phases of MIST

2.1.1. Briefing

Every simulation began with learning objectives including both technical and non-technical skills and discussion about an event that was yet to happen or a hypothetical case. The technical skills included correct techniques for specific procedures and MR

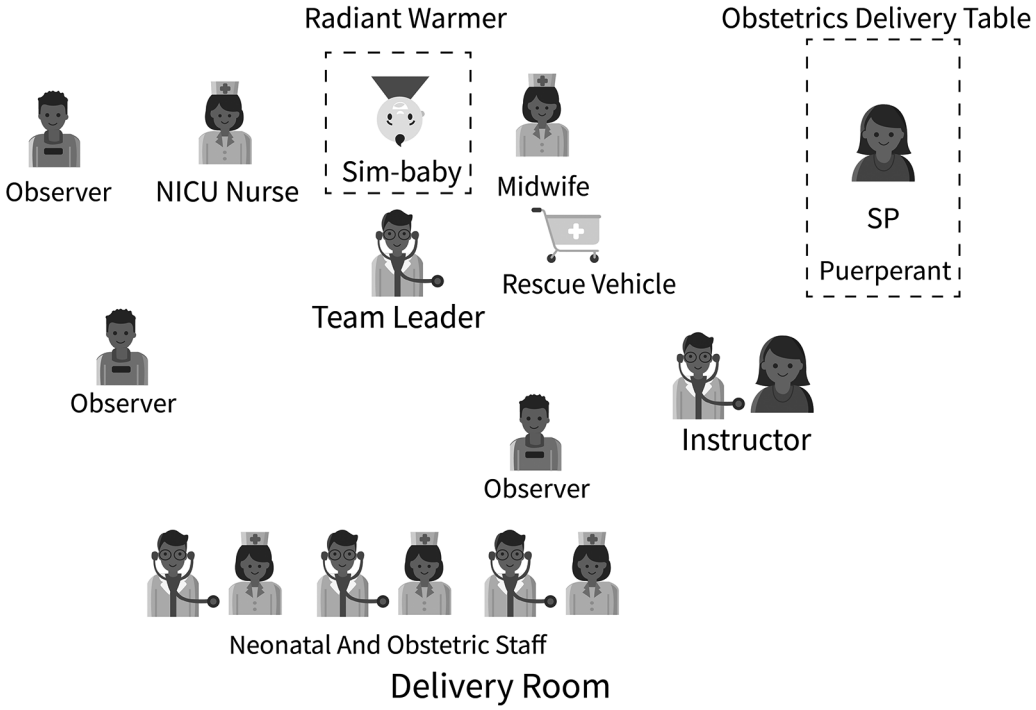

FIGURE 1
Site layout of in-situ neonatal resuscitation in HKU-SZH. The simulation was set in the delivery room or other clinical environment. Resuscitation providers included a NICU physician (usually as the leader), midwife, NICU nurse, and NICU second-line doctor according to the situation or if providers require additional help. Designated observers usually involved a NICU physician, midwife, and NICU nurse. Others included NICU and obstetric staff, trainees. SP, standardized patient.

SOPA ventilation corrective steps (Mask adjustment, Reposition of the airway, Suction the mouth and nose, Opening mouth, increasing Pressure, and placing Alternative airway) or identification of some indications for critical steps of resuscitation. Non-technical skills mainly referred to teamwork and communication.

2.1.2. Resuscitation simulation

The team leader was supposed to identify the risk factors for resuscitation, using the checklist to prepare and assign a clear task for each team member. The practitioners performed simulated resuscitation on a neonatal manikin according to scenarios based on the 7th edition of the NRP textbook and NRP® 2015 algorithm in a real clinical environment (6, 20). Low-fidelity manikin (Laerdal® Newborn Anne) was used from January 2019 to May 2020, and high-fidelity manikin (Laerdal® SimNewB™) was used from June 2020 to December 2020. Instructors, designated observers, and other staff would not disrupt nor discuss during the progression of resuscitation. Video recording was not taken during the simulation.

2.1.3. Debriefing

The debriefing was facilitated by instructors immediately after the simulation on-site in the delivery room/postpartum ward/emergency room. If it was a simulation on neonatal resuscitation and stabilization during transport, debriefing was carried out in NICU after transportation was completed. Providers, designated observers, and other staff expressed what was done well and what needed to be improved. Evidenced-based management of the case, compliance with the NRP® guidelines, and teamwork were emphasized.

2.1.4. Conclusions

The key points were summarized by the instructors to ensure that the learning objectives were achieved.

2.2. Data collection

Hospital records and NICU clinical database were retrospectively reviewed from a January, 2017 to 31 December, 2020. We compared the incidence of neonatal asphyxia, severe asphyxia, hypoxic-ischemic encephalopathy (HIE), and meconium aspiration syndrome (MAS) before (2017–2018, epoch 1) and after (2019–2020, epoch 2) the commencement of weekly MIST. Asphyxia, low Apgar score, and severe asphyxia were diagnosed according to Chinese national guidelines (25). Asphyxia was defined as Apgar score $\leq$7 at 1 min or 5 min after birth, and umbilical arterial pH < 7.2. Low Apgar

score was defined as Apgar score ≤7 at 1 min or 5 min, whereas umbilical arterial pH ≥ 7.2. Severe asphyxia was defined as an Apgar score ≤3 at 1 min or ≤5 at 5 min after birth, and umbilical arterial pH < 7.0. The diagnosis of HIE was based on the history of perinatal asphyxia and the presence of neurologic dysfunction (26). MAS was diagnosed as respiratory distress in newborns born through meconium-stained amniotic fluid at birth, which could not be explained by other causes (27). The definition of hypothermia was based on that of the WHO, with a rectal temperature of less than 36.5 °C upon admission to NICU (28). These diagnoses were mandated to be entered and checked for accuracy in the clinical database as per hospital and government policies.

Training records of weekly MIST were prospectively collected and those from 1 January, 2019 to 31 December, 2020 were reviewed in this study. We summarize and analyze the categories and teaching objectives of the cases from clinical work, and describe the training process, advantages, and limitations of this training mode.

The primary outcome was the rate of asphyxia, asphyxia or low Apgar score, severe asphyxia, and related complications including HIE and MAS. We also described the characteristics of simulation cases and participants. The characteristics of neonates with MAS were further analyzed and compared between epoch 1 and epoch 2. In the HKU-SZH, we have adopted NRP® recommendation against routine endotracheal intubation and suction since 2017, whereas the guidelines in China continue to recommend routine laryngoscopy with intubation for endotracheal suction for non-vigorous neonates born through meconium-stained amniotic fluid (29). We were therefore interested in examining the incidence of MAS. Due to the large quantity of data and limitations in our medical database, missing information also precluded us from studying other populations in detail including asphyxia, HIE, and hypothermia.

2.3. Statistical analyses

The data were presented in mean ± SD or percentage (*n*). Differences between epochs were analyzed by Student's *t*-test for continuous parametric variables and Chi-square test or Fisher Exact test for small sample size as appropriate for categorical variables. SPSS Statistics (v.26) was used for data analyses. A *P* value less than 0.05 was considered statistically significant.

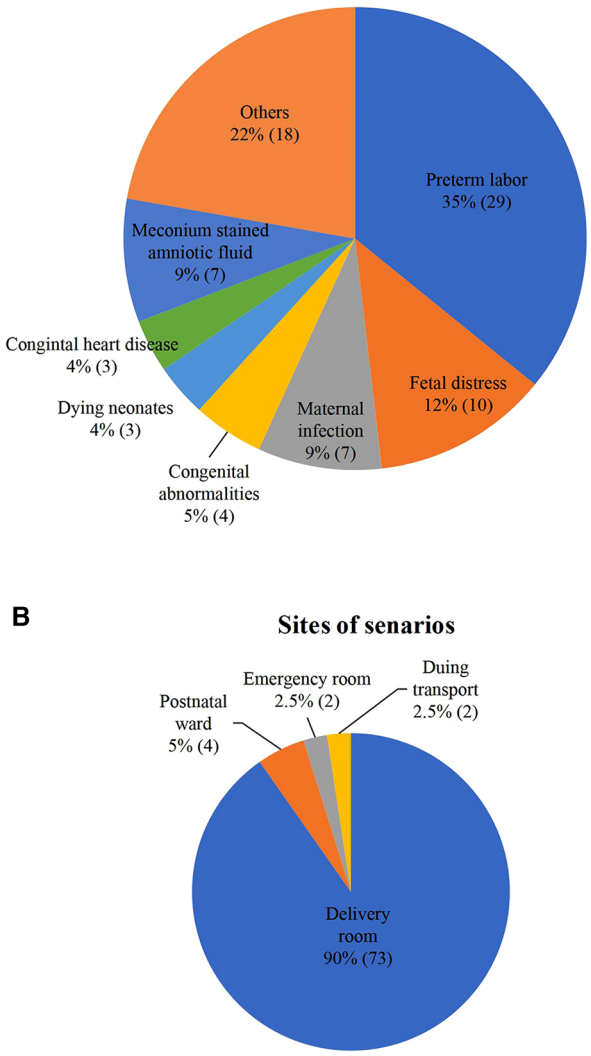

FIGURE 2
(A) Types of scenarios in 81 simulation cases. Congenital malformation included diaphragmatic hernia, digestive tract malformation; Maternal infection included acute chorioamnionitis, maternal HIV infection, maternal suspected COVID-19 infection; Others: aspiration, parents difficult to communicate with, antepartum hemorrhage, insufficient resources (manpower and equipment), maternal complications (myasthenia gravis, epilepsy), pleural effusion, pneumothorax, etc. Data are presented in % (*n*). (B) Sites of 81 scenarios. Data are presented in % (*n*).

3. Results

3.1. The weekly MIST on neonatal resuscitation

From 2019 to 2020, there were 81 sessions with simulation cases including resuscitation of preterm neonates with different gestational ages ($n = 29$, 35.8%), fetal distress ($n = 10$, 12.3%), maternal infection ($n = 7$, 8.6%), meconium-stained amniotic fluid ($n = 7$, 8.6%), and congenital abnormalities ($n = 4$, 4.9%) (**Figure 2A**). Among these sessions, 90.1% happened in the delivery room, and 9.9% in other sites including the emergency room, postpartum ward, and transport vehicle (**Figure 2B**).

There was an attendance of 1,503 participant-counts (225 active participants) in 81 simulations. The attendance included 38.5% (578) NICU physicians with working experience of more than 3 years, 21.4% (322) NICU nurses, 20.5% (308) medical trainees (NICU working experience less than 3 years or interns), 19.3% (290) midwives, and 0.3% (5) obstetricians. There were 18.6 ± 4.3 participants in each simulation. In each simulation, there were 3.3 ± 0.7 resuscitation providers, and 15.3 ± 4.3 other participants including instructors, designated observers, and other health care providers.

TABLE 1 Acute neonatal outcomes of two epochs.

	Epoch 1 ($N = 15,911$) (Jan 2017–Dec 2018)	Epoch 2 ($N = 13,848$) (Jan 2019–Dec 2020)	*P* value
Neonatal asphyxia or low Apgar score	0.97% (154)	0.8% (111)	0.128
Neonatal asphyxia	0.84% (133)	0.64% (88)	0.045
Low Apgar score	0.13% (21)	0.17% (23)	0.445
Severe asphyxia	0.138% (22)	0.058% (8)	0.029
HIE	0.10% (16)	0.01% (2)	0.003
MAS	0.19% (31)	0.09% (12)	0.014

HIE, hypoxic-ischemic encephalopathy; MAS, meconium aspiration syndrome (based on all live births).
Data were presented as % (*n*). Chi-square test or Fisher Exact test was used in statistical analyses.

TABLE 2 Comparison of patients with MAS in two epochs.

	Epoch 1 ($N = 31$) (Jan 2017–Dec 2018)	Epoch 2 ($N = 12$) (Jan 2019–Dec 2020)	*P* value
Birth weight (g)	3,261 ± 429	3,375 ± 344	0.417[a]
Gestational age (w)	40.3 ± 1.0	40.2 ± 0.8	0.91[a]
Male	71.0% (22)	41.7% (5)	0.092[b]
Apgar score at 1 min	6.7 ± 1.7	7.0 ± 2.5	0.70[a]
Apgar score at 5 min	8.0 ± 1.5	8.3 ± 1.2	0.56[a]
Apgar score at 10 min	9.0 ± 0.9	9.1 ± 0.8	0.71[a]
Endotracheal suction	3.2% (1)	8.3% (1)	0.49[b]
Positive pressure ventilation	77.4% (24)	50% (6)	0.137[b]
Chest compressions	9.7% (3)	0% (0)	0.548[b]
Temperature at admission (°C)	36.6 ± 0.79	37.2 ± 0.66	0.022[a]
Hypothermia at admission	32.3% (10)	8.3% (1)	0.14[b]
Invasive ventilation	12.9% (4)	16.7% (2)	1.0[b]
All respiratory support	51.6% (16)	83.3% (10)	0.085[b]
Duration of ventilatory support (days)	1.8 ± 2.6	1.9 ± 1.2	0.87[a]
Persistent pulmonary hypertension of newborn	5% (2)	0% (0)	1.0[b]
Pneumothorax[c]	24% (6 of 25)	9.1% (1 of 11)	0.652[b]

Data were presented as mean ± SD or % (*n*) and analyzed by.
[a]Student's *t*-test or.
[b]Chi-square test or Fisher Exact test, respectively.
[c]Incomplete denominator due to missed data.

3.2. Acute neonatal outcomes during epoch 1 and epoch 2

During the study period, 29,759 live neonates were born in HKU-SZH (15,911 in epoch 1 and 13,848 in epoch 2). Of these live births, 8,313 (52.2%) boys and 7,598 (47.8%) girls were born in epoch 1, and 7,294 (52.7%) boys and 6,554 (47.3%) girls were born in epoch 2. Of these, 1,328 were premature infants (702 in epoch 1 and 626 in epoch 2). There was an increase in forceps deliveries of 3.7% and 8.1% in epochs 1 and 2, respectively ($P < 0.001$), with no significant differences in the rate of cesarean sections and vacuum deliveries. After MIST, there were significant decreases in the incidence of neonatal asphyxia and severe asphyxia (0.64% and 0.06% vs. 0.84% and 0.14% in epoch 1, $P = 0.045$ and $P = 0.029$; respectively), but not for the incidence of neonatal asphyxia or low Apgar score (Table 1). The incidence of asphyxia or low Apgar score in premature infants decreased from 6.27% [44/702] to 3.99% [25/626] but did not reach statistical significance ($P = 0.062$). The incidence of severe asphyxia in premature infants decreased to 0.16% [1/626] [vs. 1.14% (8/702) in epoch 1, $P = 0.041$]. The incidence of HIE and MAS also decreased to 0.01% and 0.09% (vs. 0.10% and 0.19% in epoch 1, $P = 0.003$ and $P = 0.014$; respectively) (Table 1).

We further compared the characteristics of 43 neonates who were diagnosed with MAS in both epochs. There was no difference in birth weight, gestational age, gender, Apgar scores, and delivery room management. Endotracheal suctioning of meconium-stained amniotic fluid was performed in 3.2% (1/31) before and 8.3% (1/12) after MIST ($P = 0.49$). Hypothermia (defined as rectal temperature <36.5°C) at NICU admission was found in 32.3% (10/31) and 8.3% (1/12) in epoch 1 and epoch 2, respectively ($P = 0.14$). The mean body temperature at admission was significantly higher in neonates with MAS born in epoch 2 than that in epoch 1 (37.2 ± 0.7 vs. 36.6 ± 0.8°C, respectively, $P = 0.022$). The proportion of neonates who required respiratory support for epochs 1 and 2 were 51.6% and 83.3% respectively, with non-invasive support in most neonates. There was no difference in the rates of persistent pulmonary hypertension of newborns and pneumothorax (Table 2).

4. Discussion

We reported our experience in MIST on neonatal resuscitation training in China. In this single-center study, we observed that weekly MIST was feasible and sustainable in a busy tertiary hospital and was also effective in improving acute neonatal outcomes. The 81 simulation cases in epoch 2 were extracted and modified from clinical scenarios. We believe that the mutual translation of knowledge in simulated resuscitation and clinical scenario is an optimal way to improve neonatal resuscitation training and to affect clinical outcomes.

Each simulation training was scheduled at a convenient time regularly and conducted with specific learning objectives. Preterm delivery simulation was one of the most common scenarios in the training program, accounting for one-third of all scenarios. Temperature management, lung protective, and neuroprotective strategies were reinforced in the sessions according to NRP® recommendations. Moreover, we also focused on specific objectives and individualized patient-specific preparations according to different causes of preterm labor such as early administration of antibiotics for preterm neonates with maternal chorioamnionitis. Briefing, simulation, and debriefing are integrated into the process of team training.

Simulation is an effective tool to facilitate the acquisition and maintenance of cognitive, technical, and behavioral skills to

deliver safe, effective, and efficient care to neonates (30). While simulation has no risk or threat to patients, the threat to participants has been minimized. All participants acknowledged the cultural concept that errors could occur frequently during resuscitation, and everyone should learn from mistakes (31). We noticed that at the initial stage of our program, participants were reserved and passive in the debriefing session. Once the cultural concept was adopted and a safe learning environment was ensured, participants became more willing to express and share their feelings and opinions. With a multidirectional flow of information and interactive discussion, debriefing is a critical component of the learning process with the aim of improving individual and team performance. We believe that the most important part of the learning process is neither high technology nor excessive time, but a structured method to address what occurred or not occurred in due course (32). Repeated practice may not be adequate without a feedback mechanism (33). During our debriefing practice, the feedback about subsequent management in NICU and follow-up were also updated to the obstetric team for quality improvement and interdisciplinary collaboration. In order to enhance participation and engagement, several designated observers watched the full simulation exercise to provide details of performance and behavioral skills. To our knowledge, there was no previous study identifying the effect of observers. We speculate that the feedback from designated observers may further promote mutual understanding among participants with different working backgrounds and experiences. The provider may be an observer in the subsequent simulation. Role transformation of participants could strengthen mutual understanding and enhance team cooperation.

The majority of participants were passive observers who did not benefit from actual hands-on practice in simulation-based training. During debriefing, the providers and designated observers were encouraged to express opinions first, followed by that of other participants who might also participate in the discussion and raise questions, including the reflection on their own experience and performance in the clinical situation and previous simulation scenarios. Indeed, there were some learners who did not participate in previous neonatal resuscitation workshops, making it impractical to be providers in MIST. These observers might follow the pedagogy framework of "Learn-See-Practice-Prove-Do-Maintain" (LSPPDM) and participate in a neonatal resuscitation workshop for hands-on skill training afterwards, and then participate in another MIST session as providers (34). This would be interesting if this helps the learning process, improve teamwork and retain skills.

The reduced incidence of asphyxia after weekly MIST is interesting and may be multifactorial. These factors included the sustained improvement in resuscitation skills (14), anticipation of perinatal risk and deployment of team members with appropriate skillsets based on risks assessment (35, 36), collaborative and cooperative work in risks assessment and resuscitation between NICU, midwifery and obstetrical staff (37). Interestingly, one observational study in Tanzania showed that frequent, brief (3–5 min weekly) on-site "Helping Babies Breathe" simulation training was associated with a 40% reduction in neonatal mortality at 24 h, which was attributed to the early initiation of basic steps of resuscitation (38). In our simulation scenarios without obvious risk factors, the midwife was set as the initial leader who was expected to perform timely initial resuscitation and effective PPV.

Furthermore, repeated practice helps maintain neonatal resuscitation performance, benefits teamwork behaviors, and improves skill retention (39–41). Indeed, it has been recommended that training should be repeated more frequently than once per year (42). Basic resuscitation skills and special considerations such as preterm delivery have been repeatedly emphasized during simulations. "Delayed cord clamping without delaying resuscitation" and early initiation of CPAP support were focused on in the 29 preterm delivery simulations. Specifically, during the simulation, our providers implemented initial resuscitation steps as appropriate to stimulate/facilitate/support spontaneous respirations while 30s to 60s was timed for (delayed) cord clamping. We believed that these strategies were related to the decline of asphyxia in premature infants.

Neonatal resuscitation is dynamic, complex, and challenging and requires interdisciplinary teamwork and effective communication under intense time pressure and psychomental stress. Complex tasks can lead to deviations from the NRP® algorithm and poor patient outcomes (43). Leadership, teamwork, and effective communication are key components of team performance (44). Clinical drills may help staff be better prepared and resuscitation areas fully equipped (45) with improved communication (46). We aimed to use team-simulated resuscitation to identify system problems, which may hinder the team's ability to perform resuscitation effectively. Multidisciplinary simulation training may promote the transfer of skills into the real-life setting (47), teamwork, team participation, and performance in resuscitation which is associated with improvement in neonatal care (48, 49).

Resuscitation training can happen in a simulation center or *in situ*. Simulation centers may not always be available or practical in low- and middle-income areas. In-situ simulation has the advantages of low-cost, increasing sense of realism, identifying latent system threats and potential risks, increasing participation of staff, and addressing specific issues in the institution (23, 50). In-situ simulation does not only refer to a clinical environment, but should also be integrated with the staff who work there with accessible information and technology (49). The scenarios were therefore designed based on real clinical events and according to institutional team composition.

Although participants might be more satisfied and confident with high-fidelity manikins, the overall performance in teamwork and integrated skills station had little advantages over the low-fidelity manikins (51). The model of MIST described in this report was effective and could be performed in resource-limited settings without high technology. Of note, there were many participants in our study, with an average of 18 in each simulation, including 3 providers and 15 healthcare professionals observing the scenario. The number of participants might have increased stress levels and reduced the training effect. With sufficient time and space, video-assisted recording and broadcasting from the resuscitation room to another separate room where observers are located may be useful in future training.

4.1. Challenges

There were a few challenges in the MIST sessions. Although there was no detailed data, the cancellation rate of the MIST sessions was not high. The simulation was scheduled at the same time every week, when the least elective clinical activities happened that facilitated attendance and avoided interruptions, with assigned providers and alternate staff to avoid non-attendance due to the increased patient volume or other unforeseen circumstances. To address concerns related to supply and equipment, many clinical materials such as endotracheal tubes, face masks, and umbilical catheter packages were reused for education after thorough cleaning and sterilization, making the training economically sustainable in developing countries. Of note, despite the effort of instructors and emphasis on the Vegas principle, the open training environment and large group size pose challenges to ensure the psychological safety of participants, especially the providers. We planned to perform quality improvement surveillance in the MIST program including the assurance of psychological safety.

4.2. Limitations

There are several limitations to this study. This is a retrospective before-after intervention study in a single center. The historical group is not an ideal control group. We were not able to distinguish other possible confounders which may have led to changes over time including the possible improvement in obstetric care, decreased birth rate, and the health of neonates. Collaboration between the obstetrical unit and NICU is important and involves regular joint departmental meetings and other interdisciplinary training, in addition to the weekly MIST. It is therefore unlikely to isolate the effects of simulation alone on neonatal outcomes. The Chinese definitions of neonatal asphyxia and severe asphyxia were different from those used internationally (25). Umbilical blood gas analysis was not available in some rural areas, so the diagnosis of a low Apgar score in this situation was also considered asphyxia in China. The diagnostic scheme for neonatal asphyxia recommended by the consensus is a dual-track system in China (24). Further, the incidence of MAS was based on the live births rather than neonates born through meconium-stained amniotic fluid because the number of neonates with meconium-stained amniotic fluid was not recorded. To improve and ensure the sustainability of MIST, teamwork assessment and objective post-simulation questionnaire including psychological safety should have been performed.

5. Conclusions

MIST on neonatal resuscitation is an effective training method to improve neonatal outcomes with decreased rates of neonatal asphyxia, severe asphyxia, HIE, and MAS. Implementation of regular and effective resuscitation training through the collaboration between departments promoted the development of neonatal resuscitation and improvement in patient safety. Additional well-designed, prospective research is needed to evaluate the effect of MIST on neonatal resuscitation in short- and long-term clinical outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of the University of Hong Kong-Shenzhen Hospital (HKU-SZH), China. This is a retrospective study of the clinical outcomes of NICU from the hospital database of 2017-2020, no informed consent was required for patients in ethical review as approved by institutional review board of HKU-SZH. The weekly MIST is an educational program that all participants were informed of the collection of training data for educational improvement or research purposes with all personal information anonymized and not disclosed.

Author contributions

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted and (4) agreement to be accountable for all aspects of the work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1138633/full#supplementary-material

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Experience in prenatal ultrasound diagnosis of fetal microtia and associated abnormalities

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Objective: Prenatal ultrasound features, associated anomalies and genetic abnormalities of microtia cases were analyzed to explore the feasibility and value of prenatal ultrasound for the diagnosis of microtia.

Methods: The ultrasonographic features, associated anomalies, chromosome examination results and follow-up results of 81 fetuses with congenital microtia were analyzed retrospectively.

Results: Among the 81 fetuses with microtia diagnosed after birth, 2 cases were missed diagnosis on prenatal ultrasound, and 1 case was diagnosed as unilateral microtia by prenatal ultrasound but was found to be bilateral microtia after birth. Microtia was accompanied by an accessory auricle in 4 cases (4.94%) and low-set ears in 7 cases (8.64%). 22 cases (27.16%) were complicated with other structural anomalies, including 11 cases (13.58%) of cardiac anomalies, 7 cases (8.64%) of ultrasonographic soft marker anomalies, 6 cases (7.41%) of facial anomalies, 6 cases (7.41%) of nervous system anomalies, 3 cases (3.70%) of urogenital system anomalies, 3 cases (3.70%) of digestive tract anomalies and 2 cases (2.47%) of limb anomalies. Chromosome karyotype analysis and gene detection were performed in 44 cases. Trisomy 18, trisomy 13, trisomy 21, pericentric inversion of chromosome 9, partial loss of heterozygosity on chromosome 14, 22q11 microdeletion and a normal karyotype were found in 2 cases, 2 cases, 3 cases, 1 case, 1 case, 1 case, and 34 cases, respectively.

Conclusion: In summary, microtia is often accompanied by congenital defects of other organs and structures, especially the heart and face, and prenatal ultrasound diagnosis of microtia and associated anomalies is of important clinical significance.

KEYWORDS

microtia, ultrasonic soft index, prenatal ultrasound, associated anomalies, genetic abnormalities

1. Introduction

Congenital microtia is a common congenital malformation presenting with external birth defects, which are also often accompanied by atresia and stricture of the external acoustic meatus and middle ear deformity, leading to conductive deafness and affecting the development of hearing and language. An external auricle length less than twice the standard deviation of the mean fetal auricle length at the same gestational age indicates microtia (1, 2).

Fetal ear examination is not a routine item in prenatal ultrasound screening, but microtia and associated anomalies can be detected by prenatal ultrasound, thereby guiding patients to receive targeted screening and providing a basis for prognostic evaluations of fetuses with microtia.

In this study, fetuses with microtia in our study site from July 2017 to July 2022 were retrospectively analyzed, and ultrasound features, common associated anomalies, and genetic features are summarized.

2. Materials and methods

2.1. Patients

Fetuses diagnosed with microtia by postnatal diagnosis in our hospital from July 2017 to July 2022 were selected.

The inclusion criteria were as follows: (1) fetuses whose mothers had a definite gestational age (determined by the last menstrual period and ultrasound in the first trimester), (2) those diagnosed with microtia that was confirmed after birth or induced labor, and (3) those with good-quality images that could be retrospectively analyzed. 81 fetuses meeting the diagnostic criteria for microtia by prenatal ultrasound were included in the study. Two cases were missed by prenatal ultrasound. One case was one of monochorionic diamniotic twin pregnancies, and the other 80 cases were singleton pregnancies. The median age of the pregnant women was 30 years (19 ~ 39 years), and the median gestational age at diagnosis was 24^{+1} weeks ($15^{+1} \sim 33^{+3}$ weeks).

2.2. Image acquisition

Ultrasonography was performed using a Voluson E10 ultrasonography machine (GE Healthcare, Zipf, Austria), with a RAB2-5 (2.5 ~ 5 MHz) transabdominal volume convex probe.

Pregnant women were placed in the supine position under obstetric conditions. The structural development of the fetuses was systematically screened by ultrasound, and biological diameters were measured. In our study site, fetal auricles were generally observed on the parasagittal plane of the temporal bone, and the probe was deflected left and right on the sagittal plane of the fetal brain or face to display the bilateral auricles. Multiplane scans (including the coronal plane and cervical posterior transverse oblique plane) and 3D imaging were further performed in cases with suspected auricle abnormality (Figure 1).

2.3. Methods

The position, symmetry, size and shape of the bilateral auricles were observed. If the above structures of the fetus failed to be observed due to fetal position, the pregnant woman was instructed to change her position or wait for the fetus to turn to an observable position. In cases of suspected microtia, the length of the auricle was measured 3 times and averaged. The principle of minimum energy for prenatal ultrasound diagnosis was followed.

The cases meeting the inclusion criteria were screened, as summarized in Table 1 and their ultrasound images were retrospectively analyzed. The following variables were analyzed and summarized: maternal age, gestational age at diagnosis, ultrasound features, associated anomalies, and genetic features.

3. Results

As indicated in research literature on the standard for the normal diameter of the fetal auricle, an external auricle length less than twice the standard deviation of the mean fetal auricle length at the same gestational age indicates microtia (1). In this study, all 81 cases met the diagnostic criteria for microtia and were accompanied by varying degrees of morphological abnormalities. Microtia can be morphologically classified into 4 types from mild to severe: type I: mild deformity and a slightly small auricle with a clear structure; type II: moderate deformity and a small auricle with a partially preserved structure (Figure 2); type III: severe deformity with only partial auricular cartilage and earlobe

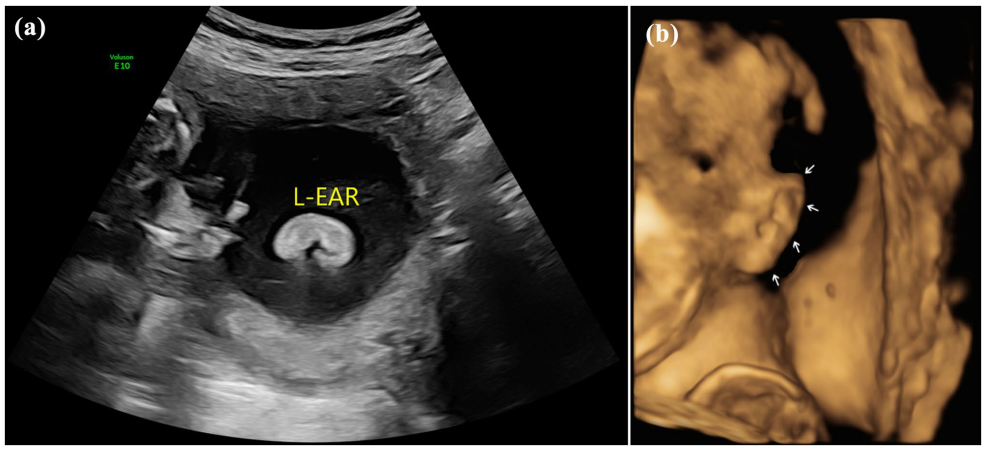

FIGURE 1
Images of normal fetal ear: **(A)** 2D sonography and **(B)** 3D sonography.

preserved, accompanied by atresia of external acoustic meatus (Figure 3); and type IV: anotia with atresia of the external acoustic meatus.

Among the 81 fetuses with microtia diagnosed after birth or induced labor, 2 cases were missed diagnosis on prenatal ultrasound, and 1 case was diagnosed as unilateral microtia by prenatal ultrasound but was found to be bilateral microtia after birth. The concordance rate of prenatal ultrasound diagnosis was 96.3%. Bilateral microtia was found in 2 cases and unilateral microtia in 79 cases, including 1 case of grade I, 17 cases of grade II, 62 cases of grade III and 3 cases of grade IV. Microtia was accompanied by an accessory auricle in 4 cases and low-set ears in 7 cases.

Twenty-two cases (27.16%) were complicated with other structural anomalies, including 11 cases (13.58%) of cardiac anomalies, 7 cases (8.64%) of ultrasonographic soft marker anomalies, 6 cases (7.41%) of facial anomalies, 6 cases (7.41%) of nervous system anomalies, 3 cases (3.70%) of urogenital system anomalies, 3 cases (3.70%) of digestive tract anomalies, and 2 cases (2.47%) of limb anomalies, as shown in Table 2.

Chromosome karyotype analysis and gene detection were performed in 44 cases. Trisomy 18, trisomy 13, trisomy 21, pericentric inversion of chromosome 9, partial loss of heterozygosity on chromosome 14, 22q11 microdeletion and a normal karyotype were found in 2 cases, 2 cases, 3 cases, 1 case, 1 case, 1 case, and 34 cases, respectively.

TABLE 1 Types of 81 fetuses with congenital microtia.

Type of microtia	*n*	Complicated with other structural anomalies (*n*)	Genetic abnormalities (*n*)
I	1	0	0
II	17	6	1
III	62	14	9
IV	3	2	0

Bilateral microtia was found in 2 cases and unilateral microtia in 79 cases. Forty four cases performed chromosome karyotype analysis and gene detection.

4. Discussion

The external ear consists of the auricle and the external acoustic meatus. As important auditory organs, the auricle and the external acoustic meatus are mainly responsible for sound collection and aesthetics. The auricle is formed in the first branchial groove and the adjacent first and second branchial arches at the 5th–6th weeks of

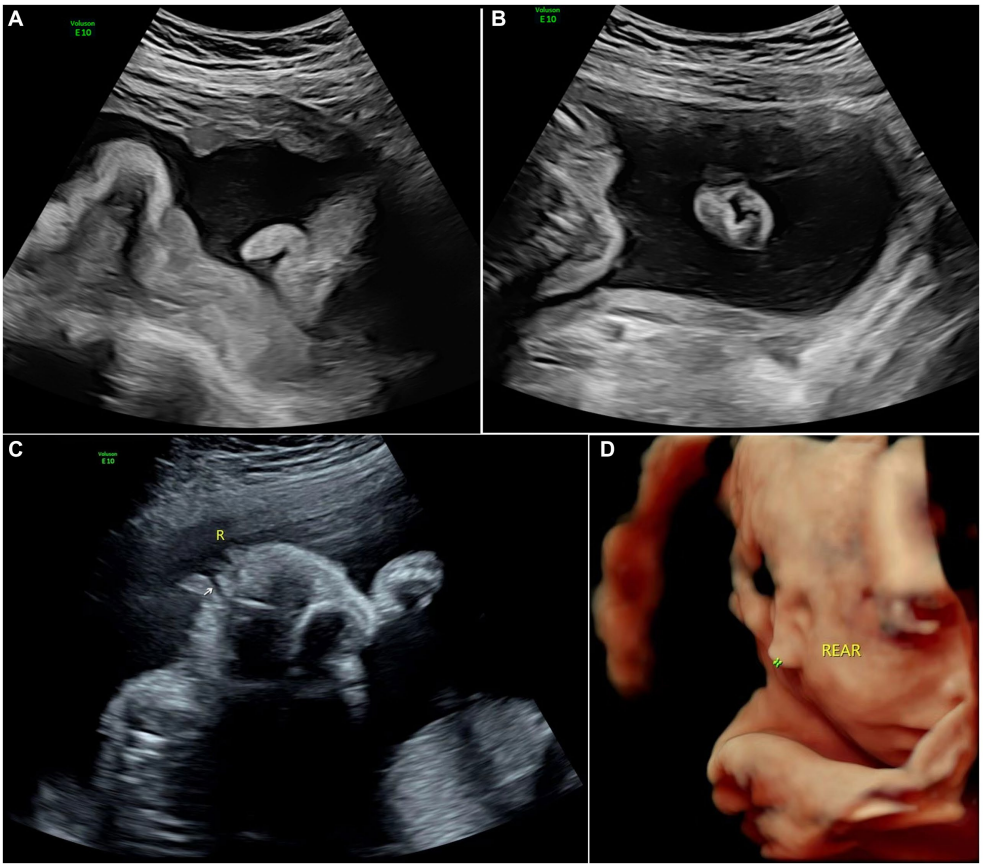

FIGURE 2
Images of type II of microtia: **(A)** 2D sonography of microtia; **(B)** 2D sonography of contralateral ear(normal); **(C)** 2D sonography of unilateral microtia type II with normal external acoustic meatus; and **(D)** 3D sonography of Unilateral microtia type II.

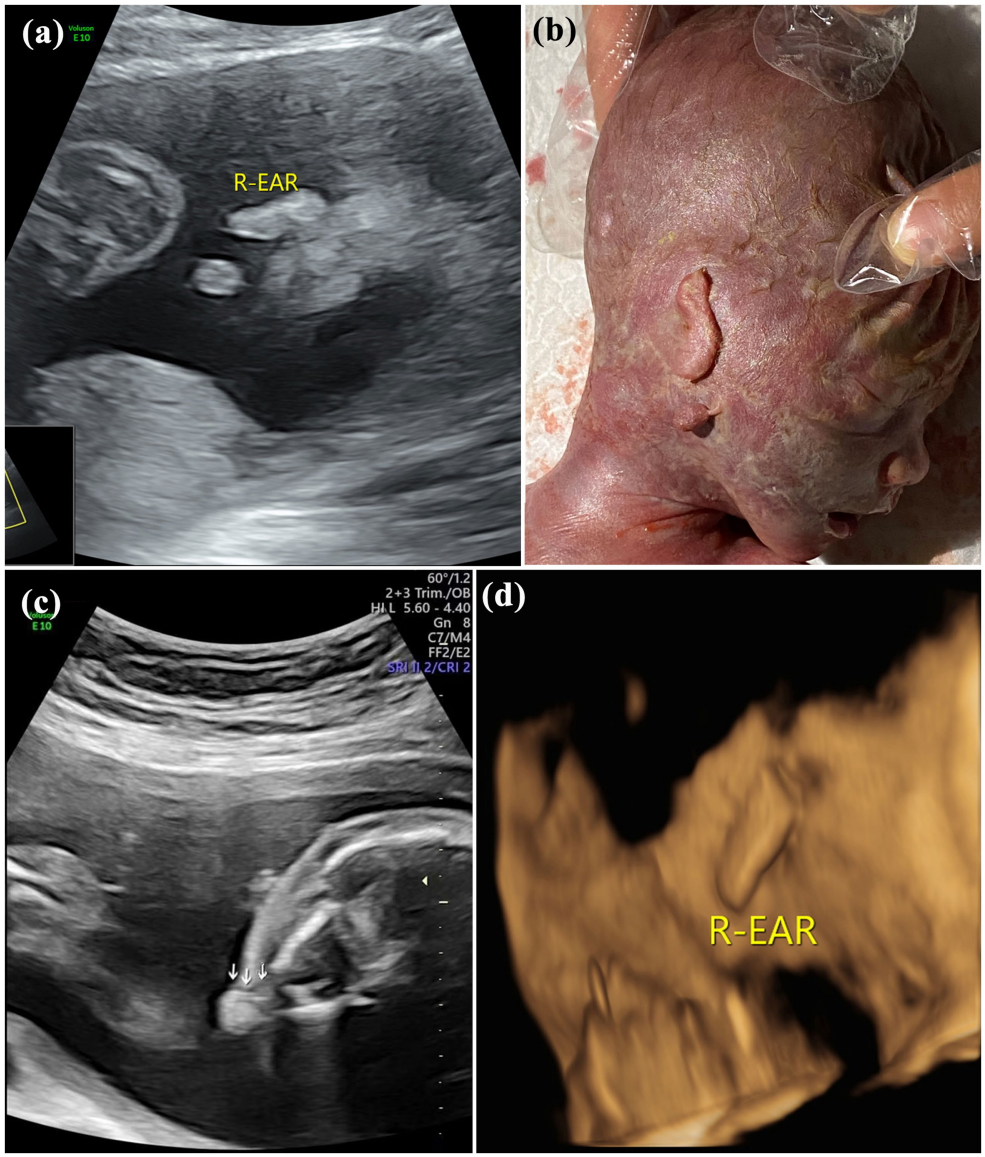

FIGURE 3
Images of type III of microtia: **(A)** 2D sonography and **(B)** photo (induced labor) of microtia type III accompanied by an accessory auricle; **(C)** 2D sonography of unilateral microtia type III accompanied by atresia of external acoustic meatus; and **(D)** 3D sonography of Unilateral microtia type III.

embryo development (3, 4). At the 20th week of embryo development, the anatomical morphology of the auricle is similar to that of adults. Blockage of this developmental process in the embryo can result in microtia characterized by a range of developmental anomalies of the auricle, including partial structural defects of the auricle and complete structural defects of the external ear, which are often accompanied by atresia of the external acoustic meatus, low-set ears and middle ear deformity along with varying degrees of conductive hearing impairment (5).

The incidence of congenital microtia in fetuses is 1‰–3‰, and the number of unilateral microtia cases is 3–5 times that of bilateral microtia cases, with unilateral microtia being more common in the right ear and in males. The incidence of microtia is positively correlated with maternal age, with an older age corresponding to a higher incidence. Due to ethnic differences, the Asian population is more susceptible to microtia (6–9).

2D ultrasound is the preferred method for fetal auricle observation. As reported in the literature, the second trimester is the best time to observe the fetal ear morphology (10). In this study, the median gestational age at diagnosis was 24^{+1} weeks, with a display rate of 97.53%, which is consistent with the conclusion in the above literature. Ultrasonically, the normal fetal auricle shows a clear and bright "C"- or "S"-type medium echo (4). The left and right auricles are symmetrical and almost equal in size. The normal auricle length measured on the parasagittal plane is linearly correlated with gestational age. The main prenatal ultrasound features of microtia include an obviously smaller length diameter of the auricle on the affected side than that on the unaffected side, disappearance of the normal auricle morphology on the affected side, which is replaced by punctate, lumpy or abnormal soft tissue echoes, and obvious asymmetry in the size and morphology of the bilateral fetal auricles on the horizontal transverse plane and coronal plane. In addition to the length of the auricles, the morphology

TABLE 2 Prenatal ultrasound features, associated anomalies and genetic abnormalities of 81 fetuses with congenital microtia.

Associated abnormality	Positive signals
Other auricle abnormality	Low-set ears
	Accessory auricle
Nervous system anomalies	Sacrococcygeal teratoma
	Vertebral anomalies
	Corpus callosum dysgenesis, Dandy-Walker
	Corpus callosum dysgenesis
Facial anomalies	Micrognathia
	Micrognathia, cleft palate
	Unilateral transverse facial cleft
	Cleft palate
Thoracic cavity anomalies	Absent thymus, pulmonary dysplasia
	Diaphragmatic hernia, congenital cystadenoma malformation
Cardiac anomalies	Double outlet of right ventricle, Ventricular septal defect
	Pericardial effusion
	Ventricular septal defect
	Ventricular septal defect, persistent left superior vena cava
	Ventricular septal defect, aortic translocation
	Coarctation of aorta
Digestive tract anomalies	Esophageal atresia
	Duodenal atresia
Urogenital system anomalies	Hydronephrosis
	Ectopic kidney
	Horseshoe kidney
Limb anomalies	Hand posture abnormalities
	Overlapping fingers
	Knee posture abnormalities
Ultrasonographic soft marker anomalies	Oedema
	Hypoplastic placenta
	Nasal bone absence
	Polyhydramnios
	Cystic hygroma of the neck
	Abnormal septa pellucida
	Single umbilical artery
	Choroid plexus cyst, nasal bone absence
	Choroid plexus cyst, polyhydramnios
	Single umbilical artery

and position of the auricles should also be observed on fetal auricle examination. In cases of fetal auricle abnormalities, the contralateral auricle should be examined carefully, and whether it is accompanied by other developmental abnormalities should be assessed. In this study, 1 case was diagnosed with unilateral microtia by prenatal ultrasound but with bilateral microtia of different degrees after birth and induced labor, and mild deformity occurred on the side with the missed diagnosis. Therefore, using the contralateral auricle as a reference for diagnosis is not recommended. Additionally, 2 cases of missed diagnosis on prenatal ultrasound were noted, but they were diagnosed after birth. According to the retrospective analysis of the images, only the unilateral auricle was shown in 1 case in the first ultrasound examination due to fetal position limitation, and the pregnant woman was instructed to undergo the examination again after a half-hour. However, the ipsilateral auricle was again mistaken for the contralateral auricle in the image. In another case, an image of the auricle was not obtained. 3D images have advantages in stereoscopic visual display of auricle deformity. However, due to the limitation of acquisition conditions including fetal position, amniotic fluid volume and other factors, 3D images acquisition was only performed in some cases.

Microtia is often accompanied by other systemic deformities. As described by Ye et al. (11) in a study involving 672 microtia patients, 1 or multiple associated abnormalities were found in 293 patients, including ear-face-neck abnormalities (40% of all associated abnormalities) and musculoskeletal system and cardiovascular system abnormalities. Research also suggests that microtia is often associated with renal dysplasia (12), with poorer auricle development corresponding to a higher risk of associated anomalies (13). Guo et al. (14) conducted a study on microtia in fetuses after birth and found that the prevalence of congenital heart disease among microtia patients is higher than that among the general population. Among the associated anomalies in this study, cardiac anomalies had the highest incidence, followed by ultrasonographic soft marker anomalies, facial anomalies and nervous system anomalies. The incidence of fetal microtia with cardiac anomalies remains high.

The pathogenesis of congenital microtia is still unclear but may involve multiple genetic and environmental factors. Microtia can be caused by many environmental risk factors, such as maternal anemia during pregnancy, diabetes mellitus, elderly age, multiple pregnancy and race. Some studies have also shown that tretinoin, thalidomide and mycophenolate mofetil are closely associated with microtia (15, 16).

Fetal auricle examination is not covered in prenatal ultrasound screening, but many recent studies have verified that microtia may indicate chromosomal abnormalities, especially triploidy (1). Chromosomal variations are considered to be associated with the occurrence of congenital microtia, especially in cases with multiple deformities or syndromic microtia. However, chromosomal variations have a lower incidence in nonsyndromic, isolated microtia (8).

Mortier et al. (7) performed gene detection on 44 microtia patients using single nucleotide polymorphism microarray technology. They found no pathological copy number variations that can explain the phenotype by genome-wide deletion repeat analysis using the microarray and argued that grade III microtia is the most common. Si et al. (17) found 2 cases of microtia associated with 22q11 deletion syndrome. In this study, one case of 22q11 microdeletion was found by genetic testing.

In this study, the pregnant women and their families had a less positive attitude toward genetic testing, and fetal chromosome karyotype analysis and gene detection were conducted on only a few cases; therefore, statistical analysis was performed. In addition, some studies suggest that fetal auricle abnormalities may be a new clinical indicator for intrauterine growth restriction, but more studies are required (18).

5. Conclusion

The results of this study demonstrated that prenatal ultrasound is reliable for diagnosing fetal microtia, and the second trimester is the best time to observe the fetal auricle. Unilateral fetal microtia is more common and often accompanied by congenital defects of other organs and structures, with frequent involvement of the heart and face. Soft marker anomalies are also of clinical significance.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics committee of Tianjin Medical University Ethics committee of Tianjin First Central Hospital Ethics committee of Shandong Provincial Maternal and Child Health Care Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JQ: conceptualization, writing–original draft, data collection and processing, and literature search. YR: conceptualization, writing–original draft, genetic analysis, and discussion. YG: data collection. JS: supervision, review, and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1119191/full#supplementary-material

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