ORIGINAL ARTICLE

Determining Maternal Risk Factors and Biomarkers Associated with Preterm Birth: A Multicentric Cohort Study

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ABSTRACT

Background: Preterm birth remains a significant public health challenge, accounting for around 75% of all neonatal deaths. **Aim & Objective**: To determine various risk factors along with potential biomarkers associated with preterm birth. **Settings and Design:** This prospective multicentric cohort study was conducted in two private hospitals in urban South Gujarat from January 2023 to June 2023. **Material and Methods:** Using a purposive sampling method, a total of 150 women aged 20 to 45 years were initially screened. After applying the eligibility criteria, 48 were excluded, and 102 participants were ultimately enrolled in the study. **Statistical analysis used:** Chi-square test was used to compare distribution of variables, univariate analysis to evaluate associations, odds ratios and 95% confidence intervals (CI) with P values were used. **Results**: From 102 participants, 21 (20.6%) were preterm and 81 (79.4%) were full- term. Steroid use (OR 3.28, P=0.03), history of dysmenorrhea (OR 5.26, P < 0.01), twin pregnancy (OR 14.83, P < 0.01), Individuals with an abnormal BMI were over three times more likely to experience preterm birth, and this link was found to be statistically significant (OR 3.12, P = 0.03). History of abortion had higher odds (OR 2.05). Biomarkers like Abnormal AMH (OR 3, P = 0.21), low progesterone (OR = 8.19, p < 0.01), Abnormal prolactin (OR = 8.86, p < 0.01), Abnormal ferritin (OR 36, P < 0.01) were associated with the preterm birth. **Conclusions**: Usage of steroids, dysmenorrhea, abnormal BMI and twin pregnancy are risk factors of preterm birth. Serum ferritin, prolactin and serum progesterone were identified as potential biomarkers which can be used to predict preterm birth and had positive association from study findings.

KEYWORDS

Preterm Birth, Cohort Study, Maternal Risk Factors, South Gujarat, Biomarkers

INTRODUCTION

Preterm birth (PTB) is defined as delivery before 37 weeks of pregnancy, or less than 259 days from the start of the last menstrual period. PTB is commonly grouped into three types: extremely preterm (under 28 weeks), very preterm (28 to under 32 weeks), and moderate preterm (32 to under 37 weeks). The NFHS-5 (2019–21) reports that the overall prevalence of preterm birth in India is approximately 12.4%. PTB increases the risk of both short- and long-duration health problems. It is the commonest cause of newborn death and the second highest contributor of death in children below five. PTB is also tied to higher medical costs and long-term social and economic challenges. (2)

Key drivers for preterm delivery include a previous history of PTB, twin delivery, short cervix detected on mid-trimester transvaginal ultrasound, low socioeconomic and educational status, inadequate prenatal care, maternal infections, uterine abnormalities, second-trimester surgery, depression, smoking, drug use, and older maternal age. (3).

Until now, cervical length has been the primary tool for predicting preterm birth, with a shorter length (<30 mm) considered a warning sign. However, this method has limited sensitivity and specificity, reducing its reliability(4). Various maternal, biochemical, demographic, and behavioural factors have been explored to predict preterm delivery, but none have proven consistently effective.(5) this highlights the need for a reliable marker that can offer clear insight into the risk of preterm birth.

Aim & Objective(s): The primary objective of the study was to determine maternal risk factors and assess potential biomarkers associated with preterm birth

MATERIAL & METHODS

This prospective cohort study was executed in the one of the city of South Gujarat for the period of 6 months (January 2023 to June 2023). Participants were selected from the hospitals of two different renowned private gynaecologists. The hospitals were selected based on their high patient volume and willingness to collaborate in the study during the study period. The participants were from economically stable families and were able to afford the hospital charges. Before starting the study, we made sure to follow all the necessary ethical guidelines and obtained approval from Institutional Human Ethics Committee with protocol number MPC/IHEC/03/2022.The study was approved on 24th of December 2022. Informed written consent was taken before enrolling the participants. Pregnant women with age of 20 to 45 years and women who has delivered and lactating mother not more than a week were included in the study and Women in first trimester, pregnant using donor eggs or sperms and had infertility issues to the male partner were excluded. By using non probability purposive sampling method, total 150 participants were screened and selected at first. 48 women were excluded from the study owing to falling in the exclusion criteria and 102 participants were enrolled in the study. No loss to follow-up was reported amongst enrolled women. Follow up of the participants were done two months apart from the date of enrolment to delivery. Serum levels of AMH, ferritin, prolactin, and progesterone were tested using standard lab methods and reference values(1) and The WHO BMI categories (Underweight: <18, Normal: 18–24.9, Overweight: 25–29.9, Obese: ≥30 kg/m²) were used. Results are shown as odds ratios with 95% confidence intervals and p - values. Chi-square test was used. SPSS software (version 22) was utilized for data analysis.

RESULTS

This study's results are based on the observations of 102 participants. From 102 participants enrolled in the study, 21 (20.6%) were preterm births and 81 (79.4%) were full- term births. Percentage of each table was calculated individually for each risk factor and the difference in the number of n in some variable was due to non-availability and non-response of the particular question asked. Table 1 shows relationships of several risk factors with pre and full term birth. Out of 21 preterm birth, steroid was used in 16 (76.2%) of the preterm births while it was not used in 5 (23.8%). The odds ratio of 3.28 (95% CI 1.09 - 9.8) suggests that the steroid use is linked with an increased chance of preterm birth. The link was found to be statistically significant (P = 0.03). Out of total 21 preterm births 12 (57.1%) women had history of abortion while 32 (39.5%) women who had full-term births had history of abortion (OR 2.05,95% CI 0.77 - 5.39) however the association was not statistically significant (P = 0.23). similarly 8 (38.1%) women who had preterm birth had uterine cyst and 13(61.9%) women who had preterm delivery didn't have uterine cyst (OR 2.5,95% CI 0.88 - 7.05) though the odds of having PTB amongst women with uterine cyst were high, the association was not statistically significant (P = 0.14). strong and significant (P < 0.01) association was found between history of dysmenorrhea with preterm delivery with OR 5.26 (95% CI 1.87 - 14.77) suggesting dysmenorrhea is linked with an increased chance of PTB. Stronger and significant (P < 0.01) association was found between twin pregnancy and preterm birth where 13 (61.9%) women who had twin pregnancy had preterm birth in comparison to 8 (38.1%) mothers with single birth (OR 14.83, 95% CI 4.72 - 46.54). after comparing BMI in 21 preterm birth, it was found that 16 (76.2%) women had altered BMI (High/Low) in contrast to 5 (23.8%) who had normal BMI. OR of this association was 3.122 (95% CI 1.04 - 9.328) indicating the positive association between Altered BMI and preterm birth which was also found to be statistically significant (P = 0.03). Analysis of maternal age among 21 women who had preterm birth shows that 7 (33.3%) women of less than 30 years had PTB and 14 (66.7%) women of more than 30 years of age had PTB the odds ratio of 0.49 (95% CI 0.17 - 1.33) and P value of 0.24 suggested No clear connection between maternal age and the risk of delivering preterm.

Table no 2 shows the link of various biomarkers with preterm delivery. The analysis was made on the basis of availability of documents of stated biomarkers with the study participants. Many participants did not undergo the mentioned

biomarkers test which was the reason of difference in the number of participants. An association was observed between atypical AMH levels and the susceptibility to preterm labor. (OR 3, 95% CI 0.75 - 11.99) however the relation was not statistically significant (P = 0.21). Out of 20 preterm birth 7 (35%) women had low progesterone level and had preterm birth while 13 (65%) had normal progesterone (OR 8.18. 95% CI 2.25 - 29.72), this signifies the role of normal progesterone level in preventing preterm birth and the association was statistically significant (P < 0.01). Similarly out of 20 preterm births 11 (55%) women had abnormal prolactin levels and 9 (45%) had normal prolactin levels. The OR 8.86 (95% CI 2.26 - 34.77) suggests strong association between abnormal prolactin level and preterm birth which was also statistically significant (P = <0.01). After analysing role of ferritin it was found that 15 (71.4%) women out of 21 preterm births had abnormal ferritin level and 6 (28.6%) had normal ferritin, the ODDS ratio of 36 (95% CI 9.70 - 133.5) suggests very strong association between low ferritin and preterm births having strong statistical significance (P <0.01)

Table 1: Risk factors associated with Preterm Birth

	Category	Preterm Births (n, %)	Full-term Births (n, %)	Odds Ratio OR (Confidence Interval)	P Value (2-tail)
Risk Factor	Yes	16 -76.20%	40 -49.40%	3.28 (1.098 - 9.8)	0.03
Steroids Used	No	5 -23.80%	41 -50.60%		
	Yes	12 -57.10%	32 -39.50%	2.04 (0.7722 - 5.398)	0.23
History of Abortion	No	9 -42.90%	49 -60.50%		
	Yes	8 -38.10%	16 -19.80%	2.5 (0.8866 - 7.05)	0.14
Cyst	No	13 -61.90%	65 -80.20%		
	Yes	11 -52.40%	14 -17.30%	5.26 (1.876 - 14.77)	<0.01
Dysmenorrhea	No	10 -47.60%	67 -82.70%		
	Twins	13 -61.90%	8 -9.90%	14.83 (4.724 - 46.54)	<0.01
Twins/Single	Single	8 -38.10%	73 -90.10%		
	< 30 yrs.	7 -33.30%	41 -50.60%	0.49 (0.1783 - 1.334)	0.24
Maternal Age	> 30 yrs.	14 -66.70%	40 -49.40%		
	Low/High	16 -76.20%	41 -50.60%	3.12 (1.045 - 9.328)	0.03
BMI	Normal	5 -23.80%	40 -49.40%		

Table 2: Biomarkers associated with Preterm Birth

Biomarkers	Category	Preterm Birth	Full-term Birth	Odds Ratio (Confidence Interval)	P Value (2 tailed)
	Abnormal	12 (75%)	12 (50%)		
AMH				3 (0.7504 -1.99)	0.21
	Normal	4 -25%	12 -50%		
	Low	7	5		

Biomarkers	Category	Preterm Birth	Full-term Birth	Odds Ratio (Confidence Interval)	P Value (2 tailed)
Progesterone		-35%	-6.20%	8.18	<0.01
	Normal	13	76	(2.254 - 29.72)	
		-65%	-93.80%		
	Abnormal	11	4		
Prolactin		-55%	-12.10%	8.86	<0.01
	Normal	9	29	(2.258 - 34.77)	
		-45%	-87.90%		
	Abnormal	15	5		
Ferritin		-71.40%	-6.50%	36	<0.01
	Normal	6	72	(9.707 - 133.5)	
		-28.60%	-93.50%		

DISCUSSION

There are several studies proving correlation of various risk factors associated with preterm birth and at the same time there are controversial studies too where the mechanism of the associated risk factors remains unknown(6).

In the present study, 102 women were enrolled and evaluated to determine risk factors and biomarkers associated with preterm birth. The risk factors like Age, BMI, dysmenorrhea, Singleton/ twin pregnancy, steroids use, history of abortion, cyst and biomarkers like AMH, ferritin, Prolactin and Progesterone were assessed for their correlation and association with preterm birth.

Preterm birth was associated with 2.04-Fold increased risk in participants with abortion history. In a study conducted by Swingle HM et.al(7) a statistically significant correlation was found between abortion and preterm birth. However, in present study, the association was not statistically significant.

In this study, twin pregnancies showed a 14.83 times higher risk of preterm birth. Aboulghar M et al.(8)found that the rise in multiple births corresponds with increased preterm deliveries. Twins make up a significant share of preterm and low-birth-weight births, greatly affecting perinatal health trends. Because the placenta in multiple pregnancies cover more of the uterus, risks like placental abruption or placenta previa increase, which can lead to early delivery to protect the mother and baby.

In current study, Women younger than 30 years showed a lower chance of having a preterm birth, with an odds ratio of 0.49 (95% CI: 0.20 - 1.19). However, this difference was not statistically significant (P = 0.14). Similar results were reported by Fuchs F et al (9) where he mentioned that after accounting for potential confounding factors, advanced maternal age remained linked to a greater predisposition to preterm birth, while younger mothers showed the lowest likelihood of delivering prematurely. Nevertheless, the link between advanced mother age and preterm birth continues to be debated and warrants further investigation.

Women with history of dysmenorrhea have 5.26 times more chances of having preterm birth in comparison to women with no history of the same. (95% CI 1.87 - 14.77) the association was highly significant in our study (P < 0.01). The study done by Rawlands IJ et.al (10) predicts that severe dysmenorrhea and menorrhagia occurring prior to a second or later pregnancy may be associated with a higher likelihood of preterm birth. Juang CM et al (11) in his study states that women with severe primary dysmenorrhea may face an increased likelihood of delivering preterm spontaneously. Very less is known about the exact mechanism behind this. These two disorders may share an underlying pathophysiologic mechanism. Additional in-depth research is needed to investigate this potential connection further.

Our study found that women with abnormal BMI had a 3.12- times more chance of preterm delivery (95% CI: 1.04–9.32), with this association being statistically significant (P = 0.03). McDonald SD et al (12), in his article, reported that overweight and obese women have greater chance for both spontaneous and medically induced preterm birth. Despite adjusting for publication bias, the elevated risk persisted. These results align closely with the findings of our study.

This study also examined various biomarkers and their link to preterm birth. It found that abnormal ferritin levels were strongly linked with a 36-times high risk of preterm delivery (P < 0.01; 95% CI: 9.70–133.5). Several biological pathways may explain how low ferritin, anemia, and / or iron deficiency affects pregnancy outcomes. According to Allen LH(13), anemia causes hypoxia and iron deficiency raises serum norepinephrine, both of which trigger maternal and fetal stress, leading to increased corticotropin-releasing hormone (CRH) levels—a key factor in preterm labor. CRH has

been shown to enhance fetal cortisol production, which may negatively impact the fetus's linear growth. Additionally, iron deficiency may contribute to oxidative stress within red blood cells and the fetoplacental unit. This deficiency could also heighten the chance of maternal infections, potentially leading to increased CRH secretion and increase the chance of preterm delivery. Exploring these biological pathways in anaemic and iron-deficient pregnant women would be valuable, especially since this study found a strong and significant link between abnormal ferritin levels and preterm birth. However, more such study focusing on such association is required.

In present analysis it was found that Women with low progesterone levels were significantly more likely to experience preterm birth, with the risk being over eight times higher compared to those with normal levels (OR = 8.19, p < 0.01). Progesterone may contribute to the prevention of preterm birth by modulating the expression of progesterone receptor coactivators and altering histone acetylation that controls uterine muscle contractions. It also blocks oxytocin binding and signaling by directly interacting with the oxytocin receptor in a non-genomic way. Additionally, progesterone affects immune responses both throughout the body and at the maternal-fetal interface. Recent research by Renthal N.E. et al.(14)shows it controls the myometrial expression of several miRNA-200 family members and its targets, that controls genes tied to contractions. In 3rd of February of year 2011, the FDA approved hydroxyprogesterone caproate shots to help prevent repeated preterm births risk in women with a history of spontaneous preterm birth in singleton pregnancies.(15) this marked the first FDA-approved drug specifically for preventing preterm birth during pregnancy.

We identified that women with abnormal AMH levels were having three times higher chance of preterm delivery as compared to those with normal levels. (95% CI 0.75 - 11.99) however, the association was not statistically significant. Stegmann BJ et al.(16) concluded that a lack of decline in AMH levels between the first and second trimesters, particularly when maternal serum alpha-fetoprotein (MSAFP) levels are elevated, had linkage with an increased risk of preterm birth. He suggests that tracking fluctuations in AMH levels from the first to the second trimester could aid in recognizing women who might respond positively to treatments like progesterone supplementation.

Women with abnormal prolactin levels had significantly more chances of giving birth early, with the risk being nearly nine times higher than those with normal prolactin levels (OR = 8.86, 95% CI: 2.26–34.77, p < 0.01). Like present study, Ragam AS et al (17) has also found that Cervico-vaginal Prolactin level was found to be a better predictor of preterm delivery in symptomatic women when compared to Cervico-vaginal β-hCG level. However, Mazor M et al (18) concluded that prolactin levels remained stable in relation to preterm or term parturition.

CONCLUSION

From the present study it can be concluded that usage of steroids, dysmenorrhea, abnormal BMI and twin pregnancy are the significant risk factors of preterm birth. Also, serum ferritin, prolactin and serum progesterone were identified as potential biomarkers which can be used to predict preterm birth and had strong positive association from the present study findings. Recognizing biomarkers linked to preterm birth can strengthen early risk assessment during pregnancy, helping to prevent its occurrence and lessen the health complications and fatalities it causes. There is a need for future research using larger and more diverse samples with the use of multivariate modelling.

RECOMMENDATION

Based on the study findings, it is recommended that pregnant women be regularly screened for key risk factors like abnormal BMI, history of dysmenorrhea, history of abortion, steroid use, and twin pregnancies. Simple blood tests like serum ferritin, prolactin, and progesterone can help identify those at higher risk for preterm birth. Early detection through these markers can guide timely interventions during pregnancy, which can help prevent preterm births and improve health outcomes for both mothers and new-borns.

LIMITATION OF THE STUDY

The participants in this study were selected using purposive sampling technique and primarily from urban areas, so the findings may not fully apply to women living in rural settings and generalized.

RELEVANCE OF THE STUDY

The findings of this study contribute to early identification and targeted care for at-risk pregnancies, especially in urban populations, and support improved strategies to reduce preterm birth-related complications.

AUTHORS CONTRIBUTION

All authors have contributed equally.

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Conflict of Interest

There are no conflicts of interest.

Declaration of Generative AI and AI Assisted Technologies in the Writing Process

The authors haven't used any generative AI/AI assisted technologies in the writing process.

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