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Original Article

Effectiveness of Progesterone Treatment Among Pregnant Women in a Tertiary Care Teaching Hospital

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Abstract

Progesterone is essential for the maintenance of pregnancy. Threatened abortion and recurrent miscarriage are the common complications of pregnancy. This study conducted to determine the effectiveness of progesterone supplementation in preventing miscarriage in cases of threatened abortion and recurrent miscarriages, aiming to extend pregnancy beyond 24 weeks in these women. The objectives of this study are to identify the number of pregnant women treated with progesterone, to know the choice of progesterone formulation prescribed for threatened abortion and previous history of miscarriage, and to determine the effectiveness of progesterone treatment among patients with threatened abortion and previous history of miscarriage. The results showed that a total of 107 cases were treated with progesterone, Among the majority of the cases were threatened abortion cases 50 (46.42%), followed by previous history of miscarriage cases 26 (24.29%), previous history of preterm birth cases 15 (14%), primi gravida cases 12 (11.21%) and short cervix cases 4 (3.7%). The outcome of this study determines that, out of 50 (46.42%) threatened abortion cases, 46(92%) women successfully continued their pregnancies to proceed beyond 24 weeks, and 4(8%) cases got abortion. Among 26 (24.29%) previous history of miscarriage cases 25 (96.1%) women successfully continued their pregnancies and 1(3.8%) got an abortion. It also demonstrates the rate of abortion was reduced in women treated with progesterone supplementation.

Keywords: miscarriage, preterm birth, primi gravida threatened abortion, progesterone, short cervix.

Introduction

Progesterone is an endogenous steroid hormone that is generally produced by the adrenal cortex as well as the gonads, which consist of the ovaries and the testes. The ovarian corpus luteum secretes progesterone during the first ten weeks of gestation, and the placenta follows in the later phases of pregnancy (Lou *et al.*, 2021). Progesterone possesses a variety of uses throughout pregnancy and is certainly a pivotal hormone for maintaining pregnancy. Among these are the induction of secretory changes necessary for successful implantation and maintenance of a normal pregnancy, which eases and makes the uterus's endometrium more open to the early embryo; and the induction of uterine quiescence, which suppresses myometrial contractility by enhancing nitric oxide conflation in the endometrium (Duan *et al.*, 2010).

Besides its endocrine effects, progesterone plays an immunomodulating role. Several studies have demonstrated that progesterone blocks mitogen-stimulated lymphocyte proliferation, prolongs allograft survival, modulates antibody production, decreases the oxidative burst of monocytes, reduces the production of proinflammatory cytokines by macrophages in response to bacterial

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products, and alters cytokine secretion by T-cell clones to favor IL-10 production (Szekeres-Bartho *et al.*, 2008). Low serum hCG or progesterone levels may predict first-trimester abortions (Lee *et al.*, 2017). Progesterone is an umbrella term that encompasses progestins (synthetic progestogens). This hormone may also protect by changing the mother's immune system, making the uterus less contractile, and improving blood flow between the uterus and the placenta (Voon *et al.*, 2022).

Threatened abortion, as demonstrated by vaginal bleeding, with or without abdominal cramps, is a common complication of pregnancy. It occurs in 20 percent of women during early gestation and roughly half of these pregnancies will abort (Qureshi *et al.*, 2009). Threatened abortion can result in pregnancy complications such as preterm delivery, foetal growth detainment, preeclampsia, eclampsia, premature rupture of the membrane, placental abruption, and stillbirth in subsequent pregnancies (Bataa *et al.*, 2024). Chromosomal abnormalities, Mullerian malformations, maternal illnesses, and other environmental exposures, including smoking and caffeine consumption are among the factors that can lead to a threatened abortion during the first trimester of pregnancy. The disequilibrium of the endogenous microflora triggers a stress response cascade that impedes fetomaternal tolerance and increases the hazard to pregnancy maintenance, according to additional research (Morelli *et al.*, 2015). On the other hand, it has been proposed that a likely cause of threatening abortion is insufficient immunological tolerance between the mother and the fetus (De la Rochebrochard & Thonneau 2002). In the presence of sufficient progesterone levels during pregnancy, lymphocytes synthesize a mediator called Progesterone-Induced Blocking Factor (PIBF), which is anti-abortive and also modulates the maternal immune response to prevent fetal rejection by shifting the cytokines from type 1 to type 2 cytokines and increasing the production of cytokines type 2.

The amount of interferon-alpha and interleukin-10 in the endocervical space changes when progesterone is given (Alimohamadi *et al.*, 2013). When the pregnancy continues, women who experience a threatened abortion are at increased risk of adverse pregnancy outcomes, including pregnancy loss, antepartum haemorrhage, preterm delivery, perinatal mortality, and low birth weight babies (McLindon *et al.*, 2023). Miscarriage is defined as the spontaneous loss of a pregnancy before 24 weeks gestation, and it is common, with approximately 25% of women experiencing miscarriage in their lifetime and 15%–20% of pregnancies ending miscarriage (Devall *et al.*, 2022). Miscarriage affects 0.5–1% of couples. Both fetal and maternal factors are involved in the pathophysiology of miscarriage. Fetal factors include genetic or developmental abnormalities and Maternal factors encompass uterine pathology, endocrine dysfunction, antiphospholipid syndrome, and thrombophilia disorders.

There is increasing evidence that progesterone exhibits anti-inflammatory activities that will be beneficial in the prevention of miscarriages. The rationale of this treatment is to correct putatively insufficient progesterone endometrial development or inadequate immune response to fetal antigens. Both of these are likely to contribute to the pathogenesis of spontaneous miscarriage (Szekeres-Bartho *et al.*, 2008). Risk factors for miscarriage include extremes of maternal reproductive age, lifestyle factors such as smoking and alcohol use, infections, certain medications, radiation treatment, uterine structural abnormalities, cervical incompetence, and medical conditions such as autoimmune disease, severe kidney disease, diabetes, and heart disease (Zhao *et al.*, 2024).

Materials and Methods

It is a prospective study carried out for 6 months by interviewing pregnant women with prior informed consent. Pregnant women with complications like Threatened Abortion and previous history of miscarriage from inpatient and outpatient units of the Obstetrics department of SRMC&GH prescribed with progesterone were collected. The sample size was targeted at 100 with an inclusion criterion such as patients who were willing to participate in the study and patients with vaginal bleeding in the first trimester and previous history of miscarriage, with an exclusion criterion of patients who were unwilling to participate in the study.

Ethical Clearance Statement

The study has been approved by the Institutional Ethics Committee IEC and the Certificate of Approval was submitted.

Results

Table.1. Data Summary of Threatened Abortion Cases: Patient Details and Treatment

A. Age Distribution			**B. BMI Status**		
Age Range (years)	**Cases**	**%**	**BMI Category**	**Cases**	**% of Total**
18-20	11	22%	Underweight	9	8%
21-22	11	22%	Healthy weight	20	40%
23-24	9	18%	Overweight	15	30%
25-26	8	16%	Obese	6	12%
27-28	4	8%	Anemia	19	38%
29-30	4	8%	BMI is a simple calculation that uses a person's height and weight to designate a classification. The formula is BMI = kg/m2		
31-40	3	6%			
C. Menstrual History			**D. Complications During Pregnancy**		
Menstrual Cycle Type	**Cases**	**% of Total**	**Complication**	**Cases**	**% of Total**
Regular	45	90%	Nil	22	44%
Irregular	5	10%	Hypertension	5	10%
			Hypothyroidism	4	8%
E. Past Medical History			**F. Progesterone Treatment Details**		
Medical Condition	**Cases**	**% of Total**	**Treatment Aspects and Formulations**		
No significant history	43	86%	**Formulations**	**Type**	**Cases**	**% of Total**
Hypothyroidism	4	8%	Capsules		23	46%
Preeclampsia	1	2%	Tablets		17	34%
Preeclampsia	1	2%	Capsule & Injection		5	10%
Epilepsy	1	2%	Tablet & Injection		5	10%
Hyperthyroidism & hypertension	1	2%	**ROA**	Oral	40	80%
This suggests that there was no substantial relationship between past medical history and the likelihood of pregnancy continuation in the examined population.				IM	10	20%
			Dose	200 mg	34	68%
				Others	16	32%

A total of 107 pregnant women undergoing progesterone treatment were studied, with 76 cases suitable for evaluating the impact of progesterone on threatened abortions and previous miscarriages. Among the 50 women with threatened abortion, the majority were between 18 and 26 years old, while those with a history of miscarriage were more frequently aged 25 and 26. In terms of progesterone dosage, 66% of women with threatened abortions and 84.7% of those with a miscarriage history received the 200 mg dose. Pregnancy outcomes were successful in 92% of threatened abortion cases and 96.15% of those with previous miscarriages, with most deliveries occurring through caesarean section (76.19%) and APGAR scores of 8/10 or 9/10 in 95.23% of cases. A Chi-square test revealed a significant relationship between birth type and APGAR score ($\chi^2(2) = 13.26$, $p = 0.001$.

In our study, a comprehensive analysis involved the treatment of a total of 107 cases of progesterone. These cases were categorized into distinct groups based on their clinical presentations. The largest subset comprised 50 cases, representing 46.42% of the total, characterized by threatened abortion.

Following closely, there were 26 cases (24.29%) with a previous history of miscarriage, highlighting the relevance of progesterone treatment in such scenarios. Additionally, 15 cases (14%) involved individuals with a previous history of preterm birth, while 12 cases (11.21%) encompassed primigravida cases. A smaller subset of 4 cases (3.7%) presented with short cervix conditions (refer to Table 1). Progesterone is essential for the maintenance of pregnancy. Several studies suggested that progesterone supplementation may reduce the risk of miscarriage in women with recurrent miscarriage or threatened abortion. In this study, we examined a cohort of 107 pregnant women who underwent progesterone treatment within the Gynaecology Department of a Tertiary Care Teaching Hospital. Only 76 of the 107 cases that underwent progesterone treatment were considered suitable for effectively demonstrating the impact of progesterone treatment in cases of threatened abortion and individuals with a previous history of miscarriage. The patient proforma encompassed a diverse range of parameters, including demographic details such as age, BMI, menstrual history, past medical and medication history, chief complaints, complications, and specific information regarding progesterone treatment indications, formulation type, dose, route of administration, and treatment continuation. We also meticulously recorded the delivery details, which included the birth type, baby gender, delivery type, and APGAR score.

Throughout the study period, we meticulously gathered data on 107 pregnant women who received progesterone treatment. Notably, among this cohort, 50 individuals (46.72%) presented with threatened abortion. Delving deeper into this subgroup, 11 women fell within the age group of 18-20, another 11 within 21-22, 9 within 23-24, 8 within 25-26, 4 within 27-28, 4 within 29-30, and 3 within 31-40. When examining the women with a previous history of miscarriage, the age distribution revealed that 7 women were in the 25-26 age group, 6 in the 18-20 age group, and 5 each in the 21-22 and 23-24 age groups. Smaller proportions were observed in the 31-40 age group with 2 women and in the 29-30 age group with 1 woman (Table.1.A. and Figure.1.A.).

BMI varied among different age groups in women with threatened abortion. It highlighted the importance of monitoring weight during pregnancy to potentially reduce the risk of complications. The study does not directly explore the relationship between BMI and progesterone effectiveness. General medical knowledge suggests that BMI could influence hormone metabolism, but specific studies would be required to draw definitive conclusions. However, it provides some demographic details about the study participants, including their BMI categories. Among the 50 cases of threatened abortion, the majority were of healthy weight (40%), followed by overweight (30%), underweight (18%), and obese (12%). (Refer Table.1.B and Figure.1.B.).

The study included 107 pregnant women, with 50 cases identified as threatened abortion. The majority of these women were of healthy weight (40%), followed by overweight (30%), underweight (18%), and obese (12%). Most women had regular menstrual cycles (90%) (Table.1.C and Figure.1. C.).

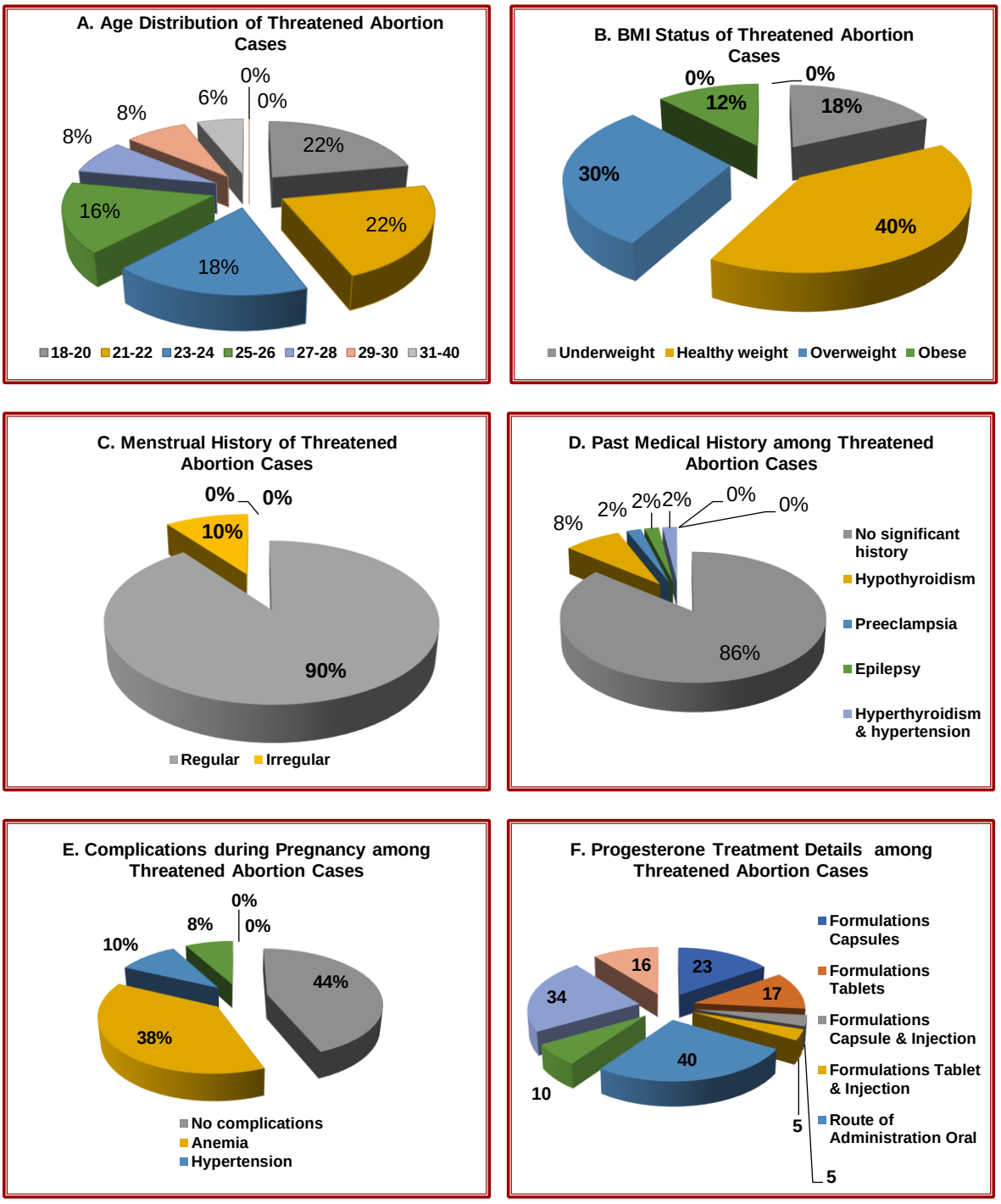
Among the 50 threatened abortion cases, 38% of women experienced complications such as anaemia, hypothyroidism (10%), and hypertension (8%). However, 44% of the women did not have any complications during their pregnancy (refer Table.1.D,E and Figure.1.D,E).

A detailed examination of progesterone prescription patterns for 50 cases of threatened abortion revealed that 46% of women received progesterone in capsule form, 34% received tablets, and 80% received the medication orally. 10% of the women received a combination of capsule or tablet with injection, while 20% received progesterone intramuscularly. Comparatively, women with a history of miscarriage received prescriptions for 54% capsules and 42.2% tablets, with a higher proportion (96.2%) receiving oral administration and only 3.8% receiving intramuscular injections (Table 1.F and Figure 1.F).

The majority of women were prescribed progesterone in capsule form (46%), followed by tablet form (34%). The most common dosage was 200 mg, administered orally in 78% of cases. Treatment continued up to the second trimester for 56% of women and up to the third trimester for 16%. (Refer Table.1.F and Figure.1.F.).

The study demonstrated that progesterone treatment was effective in reducing the rate of abortion and helping pregnancies reach term in women with threatened abortions and previous miscarriages. The study offers comprehensive insights into the demographics, treatment regimens, and outcomes of the 12 women who gave birth, of whom 75% had term babies and 25% had preterm babies. The majority of deliveries were via lower segment caesarean section (LSCS) at 96.6%, with only one normal delivery.

Figure 1: Data Summary of Threatened Abortion : Patient Details and Treatment

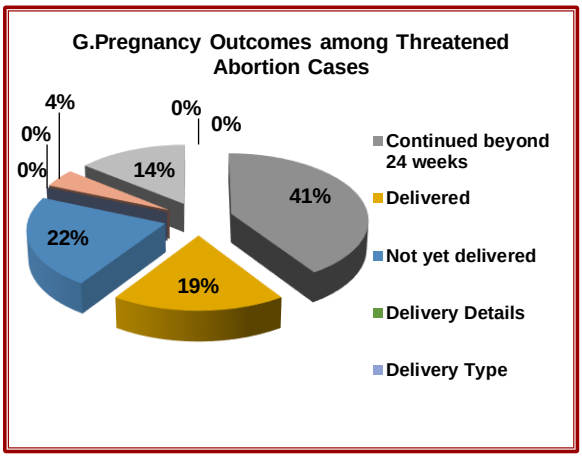


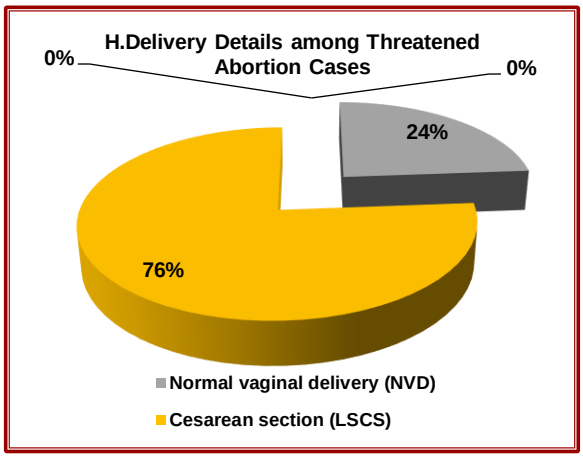
Among the 3 cases that resulted in abortion, 2 were induced, and 1 was spontaneous. (Refer Table.2. G,H,I,J and Figure.2.G,H).

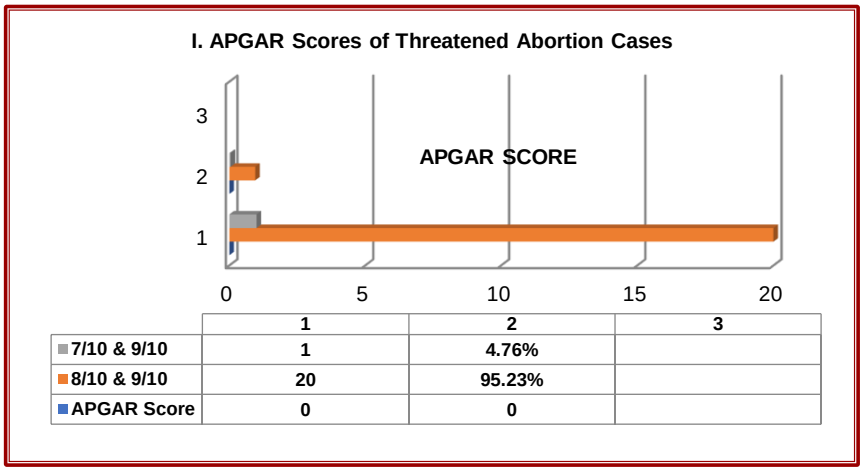
Table.2. Data Summary of Pregnancy Outcomes: Post Progesterone Treatment

G. Pregnancy Outcomes			**H. Delivery Details**		
Outcome	**Cases**	**% of Total**	**Delivery Type**	**Cases**	**% Delivered**
Delivered	21	45.60%	Normal (NVD)	5	23.80%
Not yet delivered	25	54.40%	Cesarean section (LSCS)	16	76.19%
I. Birth Details			**J. Gender of Newborns**		
Birth Type	**Cases**	**% of Delivered**	**J. Gender of Newborns**	**Cases**	**% of Delivered**
Term birth	18	85.71%	Male	11	52.38%
Preterm birth	3	14.28%	Female	10	47.61%
K. APGAR Score			**L. Chi Square Analysis**		
Score	**Cases**	**% Delivered**	**Parameters**		**P Value**
8/10 & 9/10	20	95.23%	Past medical history - Pregnancy continuation		0.755
7/10 & 9/10	1	4.76%	Complications - Pregnancy continuation		0.013
			Birth type - APGAR score		0.001
Fisher exact test was performed between Birth type and APGAR Score. There was no statistically significant relationship between birth type and APGAR Score, p =0.125.					

Figure 2: Data Summary of Threatened Abortion : Post Tretment and APGAR Score







The data on progesterone dosage in cases of threatened abortion reveals a clear preference for the lower 200 mg dose, with only a small percentage of women receiving higher doses. The first group prescribed the 200 mg dose to 34 women, while only 1 woman received the 400 mg dose. In the second dataset, the pattern holds true, with even more women (22) receiving the 200 mg dose. This further underscore the common reliance on 200 mg as the standard treatment for progesterone support in threatened abortion cases.

Moving beyond treatment specifics, the outcomes were scrutinized. Remarkably, 92% of the cases in the threatened abortion group resulted in successful term pregnancies beyond 24 weeks, with 6% resulting in abortion. Among those 92% who continued their pregnancies, 45.6% had already delivered. In the group with a previous history of miscarriage, 96.15% successfully carried their pregnancies beyond 24 weeks, while 3.8% faced abortion. Among the 96.15% who continued their pregnancies, 32% had delivered.

Among the delivered cases in threatened cases, 3 resulted in preterm births and 18 in term births. The majority of deliveries occurred through Lower Segment Caesarean Section (LSCS), accounting for 16 women, followed by Normal Vaginal Delivery (NVD) with 5 women. Additionally, 11 of the babies were male and 10 were female, with APGAR scores ranging from 8 to 9 for 20 of the babies, and 7 to 9 for 1 baby. Of the 25 women who had already given birth to their successful pregnancies, 7 gave birth to term babies and 1 gave birth to a preterm baby. The delivery details revealed that 4 of the babies were male and 4 were female, with APGAR scores ranging from 8 to 9 for 7 infants, and 5 to 8 for 1 baby.

The Chi2 test conducted in threatened abortion cases to investigate the association between birth type and APGAR score yielded statistically significant results ($\chi^2(2) = 13.26$, $p = .001$). The calculated p-value of.001 is below the predefined significance level of 5%, providing robust evidence to reject the null hypothesis. This implies a substantial relationship between the mode of birth and the APGAR scores in the analysed dataset. These results suggest that the method of delivery may significantly influence neonatal well-being, as reflected in APGAR scores. The implications of these findings warrant careful consideration in clinical practice, emphasizing the importance of tailored approaches based on birth type to optimize newborn health outcomes (Table 2. K, L and Figure 2. I).

In the study that looked at the link between birth type and APGAR score in women who had had miscarriages before, a Chi2 test first showed that the two variables were significantly linked ($\chi^2(1) = 8$, $p = .005$). However, to further scrutinize these findings, a Fisher exact test was subsequently conducted, revealing a non-significant relationship ($p = .125$). The discrepancy between the two tests raises methodological considerations, suggesting potential nuances in the data interpretation. The Fisher exact test, often used for small sample sizes, failed to corroborate these findings, despite the Chi2 test initially rejecting the null hypothesis, indicating a significant association. This incongruity highlights the importance of cautious interpretation and warrants a comprehensive examination of the study design and sample characteristics.

Discussion

In a 2024 study, researchers assigned 50 pregnancies to oral dydrogesterone and 50 to placebo. The rate of continuing pregnancy beyond 20 weeks of gestational age was 90.0% (45 out of 50 women) in the dydrogesterone group and 86.0% (43 out of 50 women) in the placebo group ($p = 0.538$) (Kuptarak & Phupong 2024). A study on previous miscarriage history reveals that out of 15 RCTs (6616 pregnancies) reporting on threatened or recurrent miscarriage, 12 (5610 pregnancies) reported on threatened miscarriage, either with or without a prior history of miscarriage. Results indicated that progesterone probably increases live births (relative risk (RR) 1.04, 95% confidence interval (CI) 0.99-1.10, absolute increase 3.1%, moderate certainty) (Zhao *et al.*, 2024) In another study, the progesterone group of 620 patients successfully prevented miscarriage in 534 cases, while 86 cases failed, resulting in a success rate of 86.13% (Lou *et al.*, 2021).

Conclusion

This comprehensive study meticulously examined the impact of progesterone supplementation on pregnant women facing threatened abortion and those with a previous history of miscarriage. We carefully assembled a cohort of 76 cases, all undergoing progesterone treatment, to explore the efficacy of progesterone. We administered either oral or parenteral progesterone (via intramuscular injection) to women who faced threatened abortion and had a history of miscarriage. Notably, out of the 50 women grappling with threatened abortion, an impressive 46 successfully sustained their pregnancies beyond the critical threshold of 24 weeks. This remarkable outcome underscores the potential of progesterone supplementation in averting abortions, with only 4 (8%) women experiencing terminations. Intriguingly, among these 4 cases, 2 (50%) women opted for induced abortion due to the absence of Foetal Heart Rate, while the remaining 2 (50%) experienced spontaneous abortions. Turning attention to the subgroup of women with a previous history of miscarriage (26 cases), a similarly encouraging trend emerged. A striking 25 women successfully carried their pregnancies beyond 24 weeks, showcasing the protective effect of progesterone supplementation. Only one woman within this group encountered spontaneous abortion, emphasizing the overall positive impact of progesterone in reducing the likelihood of pregnancy loss. In summary, this study provides compelling evidence supporting the effectiveness of progesterone supplementation in facilitating the progression of pregnancies beyond the critical 24-week mark for women facing threatened abortion and those with a history of miscarriage. Future research should focus on long-term follow-up studies to assess the outcomes of children born to mothers who received progesterone treatment. This would help understand any long-term developmental impacts on the child.

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Conflict of Interest

The authors declare that is there is no conflict of interest.

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