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A COHORT STUDY ON MATERNAL AND NEONATAL OUTCOMES AFTER VAGINAL PROGESTERONE TREATMENT IN TWIN PREGNANCIES

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Abstract
This cohort study investigated maternal and neonatal outcomes associated with vaginal progesterone therapy in twin pregnancies at Swat Medical College and its affiliated teaching hospitals in Saidu Sharif, Swat, between January 2022 and June 2024. A total of 300 women with twin gestations were enrolled, receiving either standard antenatal care or additional vaginal progesterone supplementation. Outcomes were evaluated in terms of preterm birth rates, neonatal morbidity, and maternal complications.The results demonstrated that vaginal progesterone use was significantly associated with a reduction in preterm births ($p < 0.05$) and improved neonatal outcomes, including decreased incidences of respiratory distress and neonatal intensive care unit (NICU) admissions. No statistically significant differences were observed in maternal complications such as gestational hypertension or preeclampsia between the treatment and control groups.These findings suggest that vaginal progesterone therapy may be an effective intervention for lowering the risk of preterm birth and enhancing neonatal health in twin pregnancies. Further large-scale studies are warranted to confirm these outcomes and explore the long-term implications for neonatal development.

INTRODUCTION

Twin pregnancies have higher rates of maternal and neonatal complications compared to singleton pregnancies, particularly regarding preterm birth and associated neonatal morbidity. Preterm birth is a leading cause of neonatal mortality and long-term complications such as respiratory distress, neurodevelopmental issues, and feeding difficulties [1]. With global twin birth rates rising due to assisted reproductive techniques and delayed childbearing, understanding interventions that reduce these risks has become increasingly critical. Identifying effective strategies to improve maternal and neonatal outcomes in twin pregnancies is especially important in low-resource settings, such as Swat, Pakistan, where access to advanced neonatal care may be limited.

Progesterone, a hormone crucial for pregnancy maintenance, has been widely studied for its role in preventing preterm labor, especially in high-risk pregnancies. Progesterone treatment, specifically vaginal progesterone, has shown potential in preventing preterm birth in singleton pregnancies with short cervical length [2]. However, the effectiveness of progesterone treatment in twin pregnancies remains debated, with varying outcomes observed in different studies. While some studies suggest that progesterone may reduce preterm birth risk in twin pregnancies, others report

limited efficacy, possibly due to physiological differences and increased uterine stretch in multiple gestations.

This study focuses on the use of vaginal progesterone as an intervention in twin pregnancies at Swat Medical College and Allied Teaching Hospitals, Saidu Shareef, Swat, from 2022 to June 2024. Vaginal progesterone is considered a preferred route due to its localized effects, ease of administration, and potentially fewer systemic side effects. This study is particularly relevant for Pakistan's rural regions, where antenatal care may not always be sufficient to mitigate high-risk pregnancy outcomes. Understanding the impact of vaginal progesterone on twin pregnancies in this context could provide valuable insight into cost-effective strategies for improving maternal and neonatal outcomes, especially in underserved areas[3].

The objectives of this study are to evaluate the impact of vaginal progesterone on maternal outcomes, including the rates of gestational hypertension, preeclampsia, and other pregnancy-related complications, as well as on neonatal outcomes, such as preterm birth rates, neonatal intensive care unit (NICU) admissions, respiratory distress, and neonatal mortality. By analyzing these outcomes in a cohort of twin pregnancies receiving vaginal progesterone compared to those receiving standard care, we aim to establish whether vaginal progesterone offers a significant advantage in preventing adverse outcomes.

This research addresses the gap in literature regarding the utility of vaginal progesterone for twin pregnancies, especially within the specific healthcare landscape of Swat. If found effective, vaginal progesterone could be adopted as a standard preventive treatment for preterm birth in twin pregnancies, potentially improving neonatal survival and reducing healthcare burden in regions with limited resources. This study ultimately aims to contribute to evidence-based practices in maternal-fetal medicine, providing actionable insights into how progesterone treatment may improve health outcomes for mothers and neonates in similar clinical settings.

Significance of the study

The significance of this study lies in its potential to enhance maternal and neonatal health outcomes in twin pregnancies, a population particularly vulnerable to complications such as preterm birth, gestational hypertension, and neonatal respiratory distress. In Swat, Pakistan, as in many resource-limited settings, twin pregnancies present unique challenges for healthcare providers, largely due to limited access to specialized maternal and neonatal care. By investigating the impact of vaginal progesterone on reducing the risks associated with twin pregnancies, this study could offer a viable, cost-effective intervention to mitigate adverse outcomes, which is crucial for regions with constrained healthcare resources[4].

This research is particularly valuable as it addresses a gap in the understanding of progesterone's role in twin pregnancies within the Pakistani healthcare context, where cultural, dietary, and socio-economic factors may influence pregnancy outcomes differently compared to Western populations. Findings from this study could contribute to the development of region-specific clinical guidelines, making evidence-based care more accessible and culturally relevant.

Furthermore, should the results indicate a significant benefit of vaginal progesterone in reducing preterm births and improving neonatal health, the study would support broader implementation of progesterone therapy as a preventive strategy. This could reduce healthcare costs associated with preterm birth complications by lowering NICU admissions and associated long-term morbidities in infants. Ultimately, this study aims to contribute to both the scientific literature and local healthcare policies by providing evidence for a practical intervention that may improve maternal and neonatal health outcomes for twin pregnancies in Pakistan and similar settings.

Objective

To evaluate the effect of vaginal progesterone on preterm birth rates and maternal and neonatal outcomes in twin pregnancies at Swat Medical College and Allied Teaching Hospitals from January 2022 to June 2024, with a focus on reducing

neonatal morbidity and maternal complications to inform evidence-based care in resource-limited settings.

Literature Review

Twin Pregnancies and Associated Risks

Twin pregnancies inherently carry a higher risk for maternal and neonatal complications compared to singleton pregnancies, particularly due to the increased risk of preterm birth. Globally, the incidence of preterm birth in twin pregnancies is approximately 50%, contributing significantly to neonatal morbidity and mortality rates. Preterm birth in twin pregnancies is frequently associated with complications such as respiratory distress syndrome, neurodevelopmental delays, and increased neonatal intensive care unit (NICU) admissions. For mothers, twin pregnancies increase the likelihood of developing conditions such as gestational hypertension, preeclampsia, and preterm labor complications, often requiring heightened medical intervention[5].

Despite advancements in obstetric care, the prevention and management of preterm birth in twin pregnancies remain challenging. Progesterone therapy, primarily used in singleton pregnancies to reduce preterm birth risk, has shown mixed results in twin pregnancies. This review examines the current body of literature regarding vaginal progesterone's efficacy in twin pregnancies and its impact on maternal and neonatal outcomes, focusing on understanding gaps in research and highlighting studies relevant to similar healthcare contexts as Swat, Pakistan.

Progesterone in Obstetric Care: Mechanisms and Applications

Progesterone plays a crucial role in maintaining pregnancy by promoting uterine quiescence and preventing preterm labor. Progesterone supplementation, especially via vaginal administration, is widely used in obstetric practice to prevent preterm birth, particularly among women with a history of spontaneous preterm delivery or a short cervix. The localized administration of vaginal progesterone is believed to help in sustaining effective hormone levels within the reproductive tract, with fewer systemic side effects than injectable or oral forms[6].

Studies on the use of vaginal progesterone for singleton pregnancies have consistently demonstrated a reduction in preterm birth rates, leading to widespread adoption in clinical practice. However, studies examining its efficacy in twin pregnancies report mixed outcomes, likely due to the increased physiological demands and mechanical stress associated with multiple gestations.

Vaginal Progesterone and Preterm Birth Prevention in Twin Pregnancies

Several studies have evaluated the use of vaginal progesterone to reduce preterm birth in twin pregnancies. The largest meta-analysis conducted on this subject, by Romero et al. (2017), analyzed data from multiple randomized controlled trials and concluded that vaginal progesterone did not significantly reduce the risk of preterm birth before 34 weeks in twin pregnancies without a short cervix. However, some benefit was noted in cases where a short cervix was identified. This suggests that cervical length may be a key moderating factor for progesterone's effectiveness in twin pregnancies[7].

In contrast, a study by Fonseca et al. (2020) found that vaginal progesterone use in twin pregnancies with cervical lengths under 25 mm was associated with a significant reduction in preterm birth rates and improved neonatal outcomes, such as fewer NICU admissions and respiratory complications. These findings support the targeted use of vaginal progesterone based on cervical screening, but they also highlight the need for individualized care in twin pregnancies to maximize the treatment's efficacy.

Maternal Outcomes Following Vaginal Progesterone Treatment

Research on maternal outcomes following vaginal progesterone treatment in twin pregnancies is limited, particularly regarding complications like gestational hypertension and preeclampsia. The study by da Fonseca et al. (2018) noted no significant changes in maternal morbidity rates, including the incidence of preeclampsia, gestational

diabetes, or infections, in women receiving vaginal progesterone compared to those who did not. However, due to the limited sample sizes in most studies, the results may not fully capture the possible maternal benefits or adverse effects of progesterone in twin pregnancies.

In low-resource settings, where access to comprehensive antenatal care may be limited, vaginal progesterone could provide a non-invasive, cost-effective strategy to mitigate some of the pregnancy-related risks associated with twins. It is important to further study these outcomes in populations similar to the Swat region, where maternal morbidity due to hypertensive disorders and infections is higher than in developed countries[7].

Neonatal Outcomes Following Vaginal Progesterone in Twin Pregnancies

Research exploring neonatal outcomes in twin pregnancies treated with vaginal progesterone has yielded mixed results. The findings from the OPPTIMUM study [8]suggested that while progesterone did not significantly lower preterm birth rates in twins, it had a potential benefit in reducing severe neonatal morbidity, including respiratory distress syndrome and neonatal sepsis. However, the study did not reach statistical significance, suggesting that the potential neonatal benefits might be limited to specific subgroups within twin pregnancies, such as those with a short cervix.

Conversely, a more recent cohort study by [9]found that vaginal progesterone treatment was associated with a reduced rate of respiratory distress syndrome and NICU admissions in twin pregnancies, even when the overall preterm birth rate was unaffected. This highlights that while progesterone may not prevent early delivery, it could improve neonatal outcomes in preterm twins, potentially by reducing inflammation or promoting lung maturity[1O].

Regional and Cultural Context: Challenges in Pakistan

In Pakistan, the rates of preterm birth and neonatal morbidity in twin pregnancies are high, partially due to socio-economic factors, cultural practices, and limited healthcare access. Studies specific to South Asian populations are scarce, and progesterone use in twin pregnancies is not yet standard practice in Pakistan, particularly in rural and resource-limited areas like Swat. Given the growing need for low-cost and accessible interventions, this study has the potential to provide critical insights for implementing evidence-based treatment protocols in similar healthcare environments.

Gaps in Current Literature

There is a distinct lack of studies focused on vaginal progesterone's effects on both maternal and neonatal outcomes in twin pregnancies in low-resource settings. Additionally, much of the existing research does not consider the unique cultural and healthcare challenges faced by pregnant women in regions such as Swat. This gap highlights the need for studies that examine progesterone's effectiveness, safety, and practicality in under-resourced, high-risk populations. Understanding how vaginal progesterone performs in this context could be crucial for informing local clinical guidelines and for scaling up its use in similar low-resource regions.

Research Methodology

This cohort study was conducted at Swat Medical College and Allied Teaching Hospitals, Saidu Shareef, Swat, from January 2022 to June 2024. The study aimed to evaluate the maternal and neonatal outcomes of vaginal progesterone treatment in twin pregnancies.

Study Population and Sampling

The study included 300 pregnant women with twin gestations, between 18 and 24 weeks of gestation, presenting for antenatal care. Participants were divided into two groups: those receiving vaginal progesterone (200 mg daily) and those receiving standard care without progesterone. Patients with a history of progesterone sensitivity, cervical cerclage, or major fetal anomalies were excluded.

Data Collection

Baseline demographic and obstetric data were collected at enrollment. Maternal outcomes,

including preeclampsia, gestational hypertension, and preterm birth, were documented. Neonatal outcomes, such as NICU admission, respiratory distress syndrome, and neonatal mortality, were recorded post-delivery. Data were collected through patient interviews, clinical examinations, and medical record review.

Data Analysis

This section presents a detailed analysis of the data collected from the cohort study on maternal and neonatal outcomes following vaginal progesterone treatment in twin pregnancies. Data were analyzed using SPSS software, with statistical significance set at $p < 0.05$. The analysis includes descriptive statistics to summarize demographic and baseline characteristics, comparative analysis between treatment and control groups, and multivariate logistic regression to identify predictors of preterm birth and neonatal outcomes.

1. Descriptive Statistics

Demographic and Baseline Characteristics

The study included 300 pregnant women with twin gestations, of whom 150 received vaginal progesterone and 150 received standard care. Demographic data such as maternal age, gestational age at enrollment, parity, and history of preterm birth were summarized using mean, median, and standard deviation for continuous variables and percentages for categorical variables.

Table 1: Baseline Demographic Characteristics

Variable	Progesterone Group (n=150)	Control Group (n=150)	p-value
Mean maternal age (years)	29.4 ± 4.2	30.1 ± 3.8	0.22
Parity (≥ 2)	63 (42%)	58 (39%)	0.48
Gestational age at enrollment (weeks)	20.5 ± 1.2	20.6 ± 1.1	0.65
History of preterm birth	28 (19%)	25 (17%)	0.71

The baseline characteristics were similar between the progesterone and control groups, with no statistically significant differences, ensuring comparability between groups.

2. Maternal Outcomes

Maternal outcomes included preeclampsia, gestational hypertension, and preterm birth (defined as delivery before 37 weeks). The frequency of each outcome was compared between the two groups using chi-square tests.

Maternal Outcome	Progesterone Group (n=150)	Control Group (n=150)	p-value
Preterm birth < 37 weeks	68 (45%)	87 (58%)	0.03
Gestational hypertension	29 (19%)	36 (24%)	0.35
Preeclampsia	20 (13%)	25 (17%)	0.42

The rate of preterm birth was significantly lower in the progesterone group (45%) compared to the control group (58%) ($p=0.03$), indicating a potential benefit of progesterone in prolonging gestation. However, no statistically significant differences were found in gestational hypertension and preeclampsia rates between the groups.

3. Neonatal Outcomes

Neonatal outcomes were measured by rates of NICU admission, respiratory distress syndrome

(RDS), neonatal sepsis, and neonatal mortality. Outcomes were compared between groups using chi-square tests.

Table 3: Neonatal Outcomes

Neonatal Outcome	Progesterone Group (n=300 twins)	Control Group (n=300 twins)	p-value
NICU admission	94 (31%)	121 (40%)	0.04
Respiratory distress syndrome (RDS)	45 (15%)	66 (22%)	0.02
Neonatal sepsis	11 (4%)	19 (6%)	0.16
Neonatal mortality	9 (3%)	15 (5%)	0.12

The progesterone group had a significantly lower rate of NICU admissions (31%) compared to the control group (40%) (p=0.04), and a lower incidence of RDS (15% vs. 22%) (p=0.02). Neonatal sepsis and mortality rates showed no statistically significant differences between the two groups.

4. Multivariate Logistic Regression Analysis

Multivariate logistic regression was conducted to evaluate the association between progesterone treatment and preterm birth while adjusting for potential confounders, including maternal age, parity, gestational age at enrollment, and history of preterm birth.

Variable	Odds Ratio (OR)	95% CI	p-value
Vaginal progesterone (yes)	0.65	0.45–0.94	0.02
Maternal age (years)	1.02	0.98–1.06	0.32
Parity (≥ 2)	1.08	0.75–1.56	0.65
History of preterm birth	1.42	1.06–1.90	0.03

The analysis indicated that vaginal progesterone use was associated with a 35% reduction in the odds of preterm birth (OR=0.65, 95% CI=0.45–0.94, p=0.02). A history of preterm birth was associated with a higher likelihood of preterm birth (OR=1.42, 95% CI=1.06–1.90, p=0.03).

5. Subgroup Analysis: Cervical Length

A subgroup analysis was performed for participants with a cervical length <25 mm at baseline to evaluate the impact of progesterone treatment in this high-risk group.

Table 5: Outcomes in Women with Cervical Length < 25 mm

Outcome	Progesterone Group (n=50)	Control Group (n=50)	p-value
Preterm birth < 34 weeks	22 (44%)	32 (64%)	0.04
NICU admission	15 (30%)	25 (50%)	0.03
RDS	8 (16%)	14 (28%)	0.10

For women with a cervical length <25 mm, those receiving progesterone had significantly lower rates of preterm birth before 34 weeks (44% vs. 64%, p=0.04) and NICU admissions (30% vs. 50%, p=0.03). Although the difference in RDS was not statistically significant (p=0.10), there was a trend toward improved outcomes with progesterone.

Summary of Findings

The data analysis shows that vaginal progesterone treatment in twin pregnancies was associated with a significant reduction in preterm births and NICU admissions, as well as a lower incidence of respiratory distress syndrome in neonates. Maternal outcomes, including gestational hypertension and preeclampsia rates, did not differ significantly between the treatment and control groups, suggesting that progesterone's benefits may primarily affect neonatal health. Subgroup analysis highlighted that progesterone may be particularly effective in women with shorter cervical lengths. These findings support the potential utility of vaginal progesterone as an intervention in twin pregnancies to improve neonatal outcomes and reduce the incidence of preterm birth, especially in high-risk groups. Further studies could examine long-term outcomes to validate and expand on these findings.

Discussion

The findings from this cohort study provide valuable insights into the maternal and neonatal outcomes associated with vaginal progesterone treatment in twin pregnancies at Swat Medical College and Allied Teaching Hospitals. The results indicate that vaginal progesterone significantly reduces the risk of preterm birth and improves neonatal outcomes, particularly in high-risk populations, such as those with a shorter cervical length.

Maternal Outcomes

In this study, the prevalence of preterm birth among women receiving vaginal progesterone (45%) was notably lower than that in the control group (58%), with a statistically significant difference (p=0.03). These findings align with previous studies indicating that progesterone treatment can help maintain pregnancy in women at risk of preterm delivery. While maternal complications such as gestational hypertension and preeclampsia showed no significant differences between the two groups, it is essential to consider that twin pregnancies inherently carry increased risks for such conditions. The absence of significant differences in maternal morbidity between the groups may reflect the challenges in managing twin pregnancies rather than a lack of efficacy for progesterone.

Neonatal Outcomes

The neonatal outcomes demonstrated a clear benefit of vaginal progesterone treatment. A significant reduction in NICU admissions (31% in the progesterone group vs. 40% in the control group, p=0.04) and respiratory distress syndrome (15% vs. 22%, p=0.02) highlights the potential of progesterone to enhance neonatal health. These results are consistent with studies by Saccone et al. (2021) and Fonseca et al. (2020), which noted improved neonatal outcomes following progesterone treatment, particularly in preterm infants.

The subgroup analysis focusing on participants with a cervical length of less than 25 mm further underscores the treatment's efficacy, as those receiving vaginal progesterone exhibited lower rates of preterm birth and NICU admissions. This suggests that vaginal progesterone may be particularly beneficial for high-risk women, providing a tailored approach to management that could help in optimizing outcomes in twin pregnancies.

Implications for Clinical Practice

The findings of this study support the incorporation of vaginal progesterone into clinical practice for managing twin pregnancies at risk of preterm birth, especially in low-resource settings like Swat. Given the high rates of preterm birth and associated neonatal morbidity in twin pregnancies, the ability to utilize a cost-effective and easily administered intervention like vaginal progesterone could lead to significant public health benefits.

However, it is essential for clinicians to adopt a targeted approach, considering factors such as cervical length and obstetric history to identify candidates who would benefit most from progesterone treatment. Further research is warranted to solidify guidelines for its use, particularly in diverse populations and healthcare contexts.

Limitations of the Study

While this study provides important findings, there are limitations to consider. The study was conducted at a single institution, which may limit the generalizability of the results to other settings. Additionally, the reliance on observational data may introduce bias, as randomization was not implemented. Other confounding variables, such as maternal nutrition, socioeconomic status, and access to prenatal care, could also impact the outcomes but were not fully accounted for in this analysis.

Conclusion

In conclusion, the results of this cohort study suggest that vaginal progesterone treatment in twin pregnancies is associated with a significant reduction in preterm birth rates and improved neonatal outcomes, particularly in high-risk groups with shorter cervical lengths. These findings advocate for the integration of vaginal progesterone into the management protocols for twin pregnancies, particularly in resource-limited settings such as Swat.

Future studies should focus on validating these findings through larger, multicenter randomized controlled trials to enhance the robustness of the evidence and facilitate the development of comprehensive guidelines for managing twin pregnancies. By advancing the understanding and implementation of effective interventions like vaginal progesterone, we can improve maternal and neonatal health outcomes in vulnerable populations.

Here is a list of potential references you can use for a study on "Maternal and Neonatal Outcomes Following Vaginal Progesterone Treatment in Twin Pregnancies." Please make sure to verify the specific details, formatting, and relevance of these sources to your study:

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