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Risk of Developing GDM Gestational Diabetes Mellitus in Singleton and Twin Gestation with Use of 17 Hydroxyprogesterone Caproate

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ABSTRACT

Background: The use of 17P to prevent preterm birth is well-documented, but its potential effect on the development of GDM is not well understood. **Objective:** This study was planned with object to deeply study the effect of 17P on the occurrence of GDM in pregnant women, comparing its effects to a placebo in both single and multiple pregnancies. **Methodology:** In this prospective short study, total 198 pregnant females were recruited. Study group 17P and placebo group formed thorough randomization and the gestation age was between16 to 36 weeks. The primary outcome measured was the occurrence of GDM, diagnosed via the OGTT administered during the 24th to 28th weeks of pregnancy. **Results:** GDM was observed in 16.33% of the participants in the 17P group, while it was observed in 18% of those in the placebo group, with no statistically significant differenceobserved (p=0.755). Subgroup analyses considering factors such as type of pregnancy, obesity, and history of diabetes also showed similar non-significant outcomes. **Conclusion:** The findings indicate that 17-alpha Hydroxy Progesterone Caproate does not significantly affect the development of GDM in pregnant females. These results support the continued use of 17P in pregnancies at risk of premature birth without increasing the risk of GDM.

INTRODUCTION

Gestational diabetes mellitus (GDM) is a type of glucose intolerance that is initially identified during pregnancy. This condition can present serious feto-maternal health risks. The global prevalence of GDM affecting about 7% of pregnancies (1). This condition is linked with heightened risks of preeclampsia, cesarean section, and later onset of type 2 diabetes in mothers. For infants, GDM is associated with risks such as macrosomia, neonatal hypoglycemia, and future metabolic disorders (2).

The development of GDM is caused by a combination of insulin insufficiency and resistance to meet the increased need of pregnancy. Insulin resistance typically intensifies throughout the 2nd and 3rd trimesters, largely because of placental hormones like human placental lactogen, cortisol and progesterone which interfere with the action of insulin. (3). The American Diabetes Association (2020) outlines guidelines for classifying and diagnosing diabetes, including GDM, highlighting the importance of early detection and management to reduce adverse outcomes (4).

GDM is generally screened and diagnosed during the 24-28th weeks of pregnancy through an OGTT. The American College of Obstetricians and Gynecologists (2018) endorses universal screening to identify at-risk pregnancies and allow for prompt interventions (5). Research has demonstrated that managing GDM effectively through dietary changes, regular glucose monitoring, and insulin therapy when needed can markedly decrease the associated risks (6).

The connection between GDM and future metabolic disorders is well established. According to Feig et al. (2014), women who experience GDM are at a much higher risk of onset of type 2 diabetes mellitus in the future, emphasizing the long-term consequences of this condition (7). This underscores the critical need for preventive measures and effective management strategies during pregnancy to enhance health outcomes both in the short term and long term.

17P is primarily known for its role in preventing preterm delivery in females with history of spontaneous preterm birth (8). However, its potential effects on glucose metabolism and the development of GDM are less clear. Rebarber et al. (2007) found an increased frequency of GDM in females receiving 17P for preterm birth prevention, suggesting a possible diabetogenic effect of the hormone (9). This finding necessitates further investigation into the impact of 17P on GDM development, particularly given the conflicting results in the literature.

In one study done in 2008, provided extensive data demonstrating the link between negative pregnancy outcomes and elevated blood sugar levels. Their findings emphasize the crucial importance of managing glucose levels during pregnancy to minimize these risks. (10). Similarly, Crowther et al. (2005) demonstrated that treating mild GDM can significantly improve pregnancy outcomes, supporting the need for effective interventions (11).

The rationale for investigating the potential impact of 17P on GDM stems from its known hormonal effects, primarily utilized to prevent preterm births but also potentially influencing carbohydrate metabolism. Considering the rising prevalence of GDM, which poses significant health risks to fetus and mother, and the limited effectiveness of current preventive strategies, there is a critical need to explore additional preventative measures. The ambiguity surrounding the role of progesterone and related compounds in glucose homeostasis presents an opportunity to examine whether 17P could offer a novel approach to managing or mitigating the risk of GDM, particularly given the distinct physiological challenges faced by pregnancies with singleton and multiple gestations. This research seeks to address a gap in the existing literature by systematically assessing the effects of 17P on GDM development, potentially guiding clinical practices in prenatal care and contributing to better pregnancy outcomes.

MATERIALS AND METHODS

This prospective cohort study conducted in the Department of Obstetrics and Gynecology at tertiary care hospital in Bahawalpur city from December 26, 2022, to June 25, 2023.

Pregnant females having age 18-45 years either single or twin pregnancy with <20 weeks gestation was recruited. Participants were excluded if they had a prior diagnosis of type 1 or 2 diabetes, significant medical conditions that could affect study outcomes, a history of adverse reactions to progesterone, or a BMI > 35 kg/m². The study protocol was approved by the Institutional Review Board (IRB) of the hospital. Participants of the study provide written consent prior to enrolling.

Women were prospectively assigned to treatment or placebo groups.

Participants in the treatment group were given weekly IM injections of 250 mg of 17P, beginning at the time of enrollment in study and continuing till the 36 weeks of gestation. In contrast, the placebo group was given oral supplements of Iron (60 mg) and Calcium (500 mg) daily to match the administration frequency of the treatment group, mimicking common prenatal supplementation practices.

The required sample size to detect a significant difference between the groups was calculated based on the incidence rates of GDM reported in previous studies—12.9% in the treatment group and 4.9% in the control group (Rebarber et al., 2007). (13) Utilizing an alpha level of 0.05 and aiming for 80% power, the total sample size needed was determined to be 198 participants. This calculation was performed using OpenEpi software version 3.01.

The analysis of the data was carried out using SPSS version 25. Chi-square test and logistic regression was used for data analysis.

RESULTS

The study included 198 pregnant women aged 16 to 43 years and mean age of 29.29 ± 4.684 years. The gestational age at enrollment ranged from 16 to 23 weeks, averaging 19.38 weeks (SD = 2.265), reflecting a broad range of pregnancy stages.

Comparing the incidence of GDM between the 17P group (n = 98) and the Placebo group (n = 100), it was found that GDM was developed in 16 (16.33%) and 18 (18%) participants in treatment group and placebo group. The difference in GDM rates between the groups was insignificant (p = 0.755), indicating that 17-alpha Hydroxy Progesterone Caproate does not significantly influence the onset of GDM. The proportion of participants without GDM was similar in both groups, with 83.67% in the 17P group and 82% in the Placebo group (Table 1).

In singleton pregnancies, GDM incidence was 15.07% and 20.29% in the 17P and Placebo group (p = 0.510). For twin pregnancies, the Progesterone group showed a GDM incidence of 20.00% and 12.90% in 17P and Placebo group (p = 0.493). The differences observed were insignificant, indicating that the treatment did not significantly affect the incidence of GDM in either singleton or twin pregnancies. (Table 2).

When analyzing the effect of 17-alpha Hydroxy Progesterone Caproate on GDM across obesity statuses, the incidence of GDM in obese participants was 18.75% in the 17P group and 25.00% in the Placebo group (p = 0.573). Among non-obese participants, the GDM rates were 15.15% in the 17P group and 15.79% in the Placebo group (p = 0.917), indicating that the groups did not differ significantly (Table 3).

For participants with a prior history of GDM, 18.18% in

the 17P group developed GDM compared to 35.71% in the Placebo group (p = 0.332). Among those without a previous GDM
history, the incidence was 16.09% in the 17P group and 15.12% in the Placebo group (p = 0.860). These results suggest that previous GDM history does not significantly alter the effect of the treatment on GDM incidence (Table 4).

Regarding the impact of family history of diabetes, participants with a family history showed a GDM incidence of 28.00% in the 17P group and 14.29% in the Placebo group (p = 0.190). Among those without a family history, GDM rates were 12.33% in the 17P group and 20.00% in the Placebo group (p = 0.219). These findings indicate no significant effect of family history on the influence of 17P on GDM development (Table 5).

Table 1

Comparison of GDM Status between the Progesterone and Placebo Group

Group	GDM Status		Total	P value
	Developed	Not Developed		
Progesterone group	16 (16.33%)	82 (83.67%)	98	0.755
Placebo	18 (18%)	82 (82%)	100	

Table 2

Comparison of GDM in Relation to Pregnancy Type

Pregnancy Type	Group	GDM Status		Total	P value
		Developed	Not Developed		
Single	Progesterone Group	11 (15.07%)	62 (84.93%)	73	0.510
	Placebo	14 (20.29%)	55 (79.71%)	69	
Twin	Progesterone Group	5 (20.00%)	20 (80.00%)	25	0.493
	Placebo	4 (12.90%)	27 (87.10%)	31	

Table 3

Comparison of GDM with Obesity

Obesity	Group	GDM Status		Total	P value
		Developed	Not Developed		
Obese	Progesterone Group	6 (18.75%)	26 (81.25%)	32	0.573
	Placebo	6 (25.00%)	18 (75.00%)	24	
Non-obese	Progesterone Group	10 (15.15%)	56 (84.85%)	66	0.917
	Placebo	12 (15.79%)	64 (84.21%)	76	

Table 4

Comparison of GDM with History of GDM

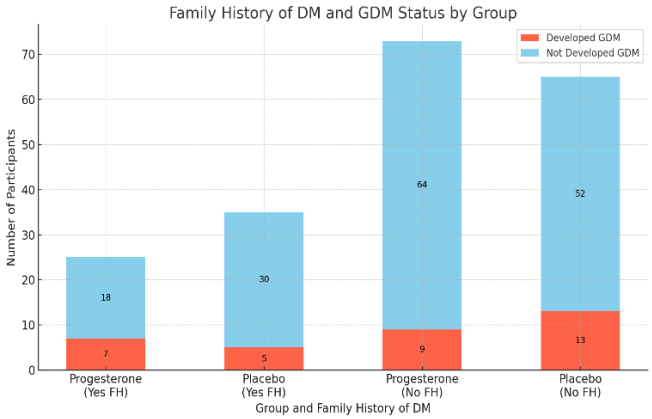
GDM History	Group	GDM Status		Total	P value
		Developed	Not Developed		
Yes	Progesterone Group	2 (18.18%)	9 (81.82%)	11	0.332
	Placebo	5 (35.71%)	9 (64.29%)	14	
No	Progesterone Group	14 (16.09%)	73 (83.91%)	87	0.860
	Placebo	13 (15.12%)	73 (84.88%)	86	

Table 5

Analysis of GDM Incidence in Relation to Family History of Diabetes among Participants in the Progesterone and Placebo Groups

Family history of DM	Group	GDM Status		Total	P value
		Developed	Not Developed		
Yes	Progesterone Group	7 (28.00%)	18 (72.00%)	25	0.190
	Placebo	5 (14.29%)	30 (85.71%)	35	
No	Progesterone Group	9 (12.33%)	64 (87.67%)	73	0.219
	Placebo	13 (20.00%)	52 (80.00%)	65	

Figure 1



DISCUSSION

The findings of this study, which evaluated the impact of 17P on the onset of GDM in pregnant women, align with several other studies while also contributing new insights to the existing body of literature. This discussion aims to contextualize these results within the broader research landscape, comparing them with findings from other relevant studies.

Firstly, the overall prevalence of GDM between the 17P and placebo groups in this study showed no significant difference (p = 0.755) which is in agreement with previous studies. Sibai et al reported in their study that 17P does not significantly alter the risk of GDM, reinforcing the notion that 17P's impact on glucose metabolism may be neutral (14).

The lack of significant difference in GDM incidence among singleton and twin pregnancies (p = 0.510 and 0.493) between the Progesterone and Placebo groups further supports this finding. Feghali et al. (2014) explored the pharmacological properties of 17P and suggested that while the drug is effective in preventing preterm births, its metabolic effects, including those related to glucose regulation, are minimal (15). This aligns with the observation that 17P does not significantly impact GDM risk in both singleton and multiple gestations.

When examining the effect of 17P on GDM incidence across different obesity statuses, this study determined that the 17P group and the placebo group did not exhibit any significant differences. (p = 0.573 for obese and p =

0.917 for non-obese participants). This result corroborates findings from Brawerman and Dolinsky (2018), who reviewed the implications of various diabetes therapies during pregnancy and noted that hormonal treatments like 17P do not significantly affect GDM incidence, regardless of the patient's obesity status (16).

Moreover, the influence of prior GDM history on the development of GDM with 17P treatment also showed no significant differences ($p = 0.332$ for those with prior GDM and $p = 0.860$ for those without). This finding resonates with the study by Hall (2011), which reviewed the effectiveness of 17P and natural progesterone in different pregnancy complications. Hall's research highlighted the need for more targeted studies to discern any potential metabolic effects of these treatments in women with previous GDM histories (17).

The investigation of GDM development relative to family history of diabetes revealed that the 17P and placebo groups showed insignificant differences. ($p = 0.190$ for those with family history and $p = 0.219$ for those without). This outcome is in line with the work of Caritis et al. (2016), which examined the role of 17P in preventing pregnancy complications and found no significant variations in GDM incidence based on familial predisposition (18).

Comparing these findings to the broader literature, it becomes evident that 17P does not significantly influence the risk of developing GDM. For instance, Badmus et al. (2020) and Olufunto et al. (2020) explored the metabolic impacts of various hormonal treatments during pregnancy and consistently found that while these treatments may affect insulin sensitivity and glucose regulation in theoretical contexts, clinical evidence does not support a significant impact on GDM incidence (19,20). This consistency across studies suggests a robust conclusion that 17P's role in GDM is minimal.

Furthermore, a study conducted by Rebarber et al. (2007) observed a higher incidence of GDM in women who received prophylactic 17P to prevent recurrent preterm delivery, which contrasts with our findings. They reported a GDM incidence of 12.9% in the 17P group compared to 4.9% in the control group, indicating a potential diabetogenic effect of 17P(13). In contrast, Gyamfi et al. (2009) conducted a secondary analysis of two randomized placebo-controlled trials and reported no significant difference in GDM rates between the groups receiving 17P and the placebo. This finding was consistent across both singleton and twin pregnancies and aligns more closely with our study's results (21).

The comprehensive safety review by Sibai et al. (2020) further solidifies this perspective. Their integrated analysis of data from major trials highlighted the favorable safety profile of 17P, noting low and comparable rates of adverse events, including GDM, between 17P and placebo groups (14). Similarly, a meta-analysis by Pergialiotis et al. (2019) found that while there was a slight increase in GDM risk with 17P, it was not statistically significant, thus supporting the overall safety of the treatment (22).

In a different systematic review and meta-analysis, Eke et al. (2019) examined the potential link between 17P and the risk of GDM. Their findings indicated an increased risk in cohort studies; however, this association was not supported by randomized controlled trials. (23). This aligns with the findings of Waters et al. (2009), who reported no significant increase in GDM rates with 17P use in a retrospective cohort study (24).

Rouholamin et al. (2015) investigated the association between 17P and gestational diabetes mellitus (GDM) in women at risk of preterm birth, concluding that there was no significant increase in GDM rates. These findings align with the results of our study, which also indicate that 17P does not significantly impact GDM risk (25).

CONCLUSION

This study demonstrates that 17-alpha Hydroxy Progesterone Caproate (17P) does not significantly impact the development of GDM in pregnant women, regardless of whether they have singleton or multiple gestations. Despite previous findings suggesting a potential diabetogenic effect of 17P, our results indicate no significant difference in GDM incidence between the treatment and placebo groups. These findings suggest that 17P can be safely used for its primary indication of preventing preterm births without increasing the risk of GDM, thereby supporting its continued use in clinical practice. Further research may be needed to explore any long-term metabolic effects and to confirm these results in larger and more diversepopulations.

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