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REVIEW ARTICLE

THE ROLE OF PROGESTERONE IN PREVENTING PRETERM LABOR: A SYSTEMATIC REVIEW

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ABSTRACT

Progesterone may help prevent premature delivery in high-risk pregnancies, according to research. Progestogens have been studied extensively and are still being studied. In women with a high-risk profile, such as those who have a history of spontaneous preterm delivery or a short cervical length (CL) on transvaginal ultrasound (TVU), prophylactic progesterone use may lower the chance of PTB. This is a systematic review investigating the effect of progesterone in preventing preterm labor, follows the PRISMA protocol. A methodical search was conducted using multiple databases of research-based literature including PubMed, Cochrane, Google Scholar, and Web of Sciences from 2000-2024. Statistical Package for Social Sciences (SPSS) version 22 was used to sort, analyze, and present data graphically. Minimum gestational age for starting progesterone therapy to reduce the risk of preterm labour and delivery was reported as 14 weeks, while end of therapy was planned until delivery. The reported incident of pre term labour, delivery and fetal death was significantly lower in patients treated with progesterone with singleton pregnancies. Preterm delivery is still a serious issue in obstetric care, impacting mothers and newborns worldwide, having significant health and economic effects for the healthcare system, individuals, and families. Limited research exists on neonatal and long-term baby health outcomes, thus it's uncertain if extending pregnancy leads to better outcomes. The purpose of this study was to assess the effectiveness of progesterone (vagina, Oral and intramuscular) in managing preterm labour to prevent, manage and reduce the risk of neonatal and maternal complications.

KEY WORDS: Delivery; labor; Multiple; Pregnancy; Pre term; Progesterone; Singleton.

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INTRODUCTION

Preterm birth is defined by the World Health Organization (WHO) as delivery that occurs before 37 weeks of pregnancy. About 85% of premature births take place between weeks 32 and 36, 10% between weeks 28 and 31, and 5% (extremely preterm neonates) before week 28.[1] One of the main causes of child death and permanent impairment is preterm birth. An estimated 15 million babies are delivered prematurely each year, with an 11% frequency worldwide.[2]

Progesterone may help prevent premature delivery in high-risk pregnancies, according to research. [3-4] Progestogens have been studied extensively and are still being studied. In women with a high-risk profile, such as those who have a history of spontaneous preterm delivery or a short cervical length (CL) on transvaginal ultrasound (TVU), prophylactic progesterone use may lower the chance of PTB.[5]

The complex etiology of preterm labor activation may make it challenging to predict. The most important predictor is an obstetric history of spontaneous preterm birth (sPTB).[6] About 35–50% of pregnancies result in sPTB, and the more spontaneous preterm births that have occurred in the past, the higher the chance of reoccurring incidents. Low socioeconomic status, maternal smoking, midtrimester cervical length <25 mm, cervical-vaginal infections, history of cervical surgery, non-Hispanic Black race, inade-

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quate prenatal care, uterine overdistension, decidual hemorrhage, and short interpregnancy interval are risk factors for this obstetric event.[7-8] Preterm delivery may occur spontaneously as a result of environmental factors, maternal anemia, periodontal disease, multiple pregnancies, ART-induced pregnancies, and epigenetics.[9] Recently, experts proposed a connection between environmental factors and preterm birth. Although the effects of pollution and other pollutants on maternal-fetal development are not well understood, a number of studies indicate that air pollution may influence epigenetic modifications.[10]

Maternal and neonatal mortality are one of the gravest concern of Pakistani healthcare community, it's been years of working on this ground however we have not achieved any Sustainable Development Goals (SDG) of maternal and neonatal health till date. To achieve SDG and reduce maternal and neonatal mortality rate its necessary to understand underlying determinants, the purpose of this study is to understand therapeutic effects of progesterone (vagina, Oral and intramuscular) in managing preterm labour to prevent, manage, treat, and reduce the risk of neonatal and maternal complications.

MATERIAL AND METHODS

This is a systematic review investigating the effect of progesterone (vagina, Oral and intramuscular) in preventing preterm labor to prevent, manage, treat, and reduce the risk of neonatal and maternal complications. Our report follows the PRISMA protocol.[11] Registration of studies protocol is not applicable. Cellular and physiological studies reporting progesterone effects on preterm birth risk were excluded from the review. Studies reporting outcome of Oral, vaginal and intramuscular progesterone in management of pre term labour were included in the study. Several databases of research-based literature, including PubMed, Cochrane, Google Scholar, and Web of Sciences, were used in a systematic search from 2000 to 2024. There were no linguistic restrictions. We employed a search strategy that included several keyword combinations in the following sequence in each of the datasets described above.

A. "Progesterone for preterm labour" [Title/Abstract]

B. "Outcomes of progesterone use to prevent preterm labour" [Title/Abstract]

C. "Progesterone outcomes in preterm labour" [Title/Abstract]

D. [A] AND [B] AND [C]

The researcher used abstracts and titles to find the most pertinent studies. The most pertinent articles were selected based on eligibility criteria after the full articles were reviewed. The important data was extracted, saved, and organized into tables. In order to address differences, two investigators retrieved the data from relevant papers, and the compression of the extracted data was examined. Any remaining discrepancies were reported by the third investigator, and each study was presented as a table with the full title, first author, publication date, study purpose/aim, study setting, study sample size, limitations, and conclusion. Data was sorted, examined, and graphically presented using the Statistical Package for Social Sciences (SPSS) version 22. All included studies included test findings of pertinent data, such as chi-square, multivariate survival analysis, time-dependent survival analysis, disease-free survival, hazard ratio, and incidence rates.

RESULTS

Total 10 articles were included in the study after careful consideration; accumulated patient count was 2496, while included study characteristics identified 09 randomized controlled trials [12-19] and 1 prospective cohort study.[20] The studies reported effect of intramuscular injections in 05[12, 14-15, 18-20], while 04 studies evaluated oral progesterone[16-17, 19, 21] effects and one had evaluated vaginal suppository[13] effects on pre term labour and delivery. (Table 01)

Table 01: Characteristics of included studies.

Publication Year	Sample size	Study design	Pregnancy
2003[12]	463	RCT	Singleton
2003[13]	157	RCT	Singleton
2007[14]	661	RCT	Twin pregnancy
2007[15]	137	RCT	Singleton
2009[16]	148	RCT	Singleton
2011[17]	33	RCT	Singleton
2013[18]	165	RCT	Twin pregnancy
2014[19]	90	RCT	Singleton
2017[20]	430	Cohort	Singleton
2017[21]	212	RCT	Singleton

Minimum gestational age for starting progesterone therapy to reduce the risk of preterm labour and delivery was reported as 14 weeks, while end of therapy was planned until delivery. Dosages of intramuscular injections were reported as 500mg – 250mg, while oral progesterone dosage was 100mg, while vaginal suppository was 100mg as well. Two studies included twin pregnancies while 08 had included singleton pregnancy. (Table 02)

Table 02: Study duration, dosage and mode of administering progesterone.

Medicine	Dosage	Start (weeks)	End
17 alpha-hydroxyprogesterone caproate (17P)	250mg	16-20	until delivery[12]
Vaginal Suppository	100mg	24	34weeks[13]
17 alpha-hydroxyprogesterone caproate (17P)	250mg	16-20	35 weeks[14]
17 alpha-hydroxyprogesterone caproate (17P)	400mg	24-30	until delivery[15]
Oral	100mg	18-24	until delivery[16]
Oral	400mg	16-20	until delivery[17]
17 alpha-hydroxyprogesterone caproate (17P)	500mg	24	31weeks[18]
Oral	100mg	24	34weeks[19]
17 alpha-hydroxyprogesterone caproate (17P)	250mg	16	20 weeks[20]
Oral	100mg	14-18	37weeks[21]

Table 03: Reported outcomes from included studies.

Publication Year	Sample size	Results	Medicine	Dosage	Start (weeks)	End	Pregnancy
2003[12]	463	RR of 0.66 for delivery after 37 week of gestation age, RR 1.15 for hospital visit due to preterm labour	17 alpha-hydroxy-progesterone caproate (17P)	250mg	16-20	Until delivery	Singleton
2003[13]	157	Significant reduction in preterm labour and delivery in progesterone group (p-value < 0.0005)	Vaginal Suppository	100mg	24	34weeks	Singleton
2007[14]	661	higher incident rate of fetal death and pre term delivery after Progesterone use (RR 1.3, 0.5-3.2)	17 alpha-hydroxy-progesterone caproate (17P)	250mg	16-20	35 week	Twin
2007[15]	137	22.5% lower cases of preterm incident with progesterone,	17 alpha-hydroxy-progesterone caproate (17P)	400mg	24-30	Until delivery	Singleton
2009[16]	148	Mean prolongation of pregnancy	Oral	100mg	18-24	Until delivery	Singleton
2011[17]	33	Decreased risk of Preterm birth at < 37 weeks of gestation	Oral	100mg	16-20	Until delivery	Singleton
2013[18]	165	No reduction in pre term labour/delivery (RR 1.04 (0.74-1.47)	17 alpha-hydroxy-progesterone caproate (17P)	500mg	24	31week	Twin
2014[19]	90	Latency to delivery: improved in oral progesterone vs placebo	Oral	100mg	24	34weel	Singleton
2017[20]	430	25% recurrence rate of preterm delivery after progesterone use	17 alpha-hydroxy-progesterone caproate (17P)	250mg	16	20 week	Singleton
2017[21]	212	Decreased risk of Preterm birth at < 37 weeks of gestation	Oral	100mg	14-18	37weeks	Singleton

The reported incidence of pre term labour, delivery and fetal death was significantly lower in patients treated with progesterone with singleton pregnancies. However the twin pregnancy had no positive reduction of pre term delivery and labour after progesterone therapy. Single study with vaginal suppository of 100mg progesterone starting at 34 weeks till 24 weeks with singleton pregnancy reported significant reduction in hospital emergency rooms visit due to preterm labour and pre term delivery as compared to control group with p-value of <0.0005.[13] The intramuscular injections of 400mg were administered in three singleton pregnancy cohorts; the reported outcome was positive association between reduced hospital visit due to pre term labour with progesterone (RR 1.5)[12], 25.5% of overall lower cases of pre term deliveries with progesterone while 25% recurrence rates were preterm delivery after progesterone use.[15] However, two twin pregnancies were reported with intramuscular progesterone the results reported higher fetal death and preterm delivery before 35 weeks of gestational age with progesterone, another twin pregnancy study reported no significant reduction of preterm labour and delivery (RR 1.04).[18] (Table 03)

DISCUSSION

Progesterone helps maintain pregnancy through many routes in the cervix, myometrium, decidua, and placenta. Vaginal progesterone supplementation has been shown to minimize the incidence of preterm birth in singleton pregnancies with a short cervix (level-1 evidence).[22] The randomized controlled studies indicated a relative risk of preterm birth of 0.58 (95% CI 0.36-0.92) and 0.55 (95% CI 0.33-0.92) in progesterone-treated groups.[23-24] Over the last 25 years, there has been a significant shift in obstetric practice and neonatal care. Maternal and baby outcomes from preterm birth studies conducted in the 1960s, 1970s, and 1980s are not comparable to more recent trials.[25-27] Da Fonseca et al[28] exclusively reported clinical outcomes for preterm births before 37 and 34 weeks of gestation. Although Meis and colleagues[29] reported on baby outcomes, the high prevalence of preterm birth (54.9%) in the control group raises concerns about the study's general applicability to the obstetric community with a history of preterm delivery. Numerous randomized controlled trials and narrative reviews have evaluated the use of progesterone in women at high risk of preterm delivery.[30-32]

In this review, reported results from singleton pregnancies with oral progesterone starting at 14-18 weeks of gestation elaborated significant reduction in risk of pre term labour incidents and pre term delivery, this result is similar to already reported multiple reviews and randomized studies of oral progesterone to assess pre term deliveries.[33-36] The overall reduction of hospital visit due to pre term labour reported significantly reduced in singleton group treated with progesterone, similar to reported literature where singleton pregnancies were reported as maintaining gestational age deliveries and proper fetal weight substantial reduction in the risk of newborn birth-weight less than 2500 g (2 trials, 501 babies, RR 0.64, 95% CI 0.49 to 0.83), but no changes were seen in secondary neonatal outcomes between the two treatment groups.[37-38]

There is inadequate information available on the best way to administer progesterone[39] this review had higher percentage of intramuscular injections and oral progesterone, while literature reported largest research on vaginal progesterone gel found no effect for women who had previously had premature delivery. This review reported lower to no effect of progesterone in reducing the risk of pre term labour or delivery; similarly, two randomized studies were included to evaluate the use of progesterone in women with multiple pregnancies. The Rouse[40] trial found no significant difference between the progesterone and placebo groups in terms of delivery before 35 weeks gestation or mortality. A large multicenter randomized placebo-controlled trial of women with twin pregnancies[41] found that giving 300 mg of progesterone twice a day from 11-14 weeks' gestation until 34 weeks' gestation did not reduce the rate of spontaneous birth between 24+0 and 33+6 weeks. There were no significant differences in pregnancy problems, fetal or neonatal outcomes, or major adverse events across the groups. More than 80% of patients took at least 80% of their pills, indicating strong treatment adherence.

This study found that initiating progesterone therapy in early pregnancy was similar to six previous smaller trials in unselected twin pregnancies. These trials found no significant effect on the incidence of early preterm birth when using lower doses of vaginal progesterone starting in mid-gestation.[42] Twin pregnancies do not benefit from universal prophylactic use of progesterone, even at high doses and starting as early as 11 weeks' gestation. Our data indicate that women with high adherence to therapy and cervical length ≥30 mm are more likely to experience spontaneous early preterm delivery, suggesting that such treatment may be detrimental.[43] Vaginal progesterone supplementation has been shown to minimize the incidence of preterm birth in singleton pregnancies with a short cervix (level-1 evidence). The two biggest randomized controlled studies indicated a relative risk of preterm birth of 0.58 (95% CI 0.36-0.92) and 0.55 (95% CI 0.33-0.92) in progesterone-treated groups.[44-45] A meta-analysis of twin pregnancies with short cervix found that cerclage was associated with an increased risk of preterm delivery.[46] Additionally, a randomized trial of high-dose 17-OHPC therapy (500 mg intramuscularly twice weekly) in unselected twin pregnancies showed an increased risk of birth before 32

weeks.[47] The discrepancies between singleton and twin studies have led to conjecture that the mechanism of cervical insufficiency and premature labor is distinct in twin pregnancies. Possible physiological explanations for this difference include elevated levels of maternal corticotrophin-releasing hormone, increased oxytocin receptor expression, and uterine distention, which can cause myometrial stretch and increase interleukin-8 levels, collagenase secretion, and gap-junction formation.[48-50]Progesterone supplementation has been shown to minimize the incidence of preterm birth in singleton pregnancies (level-1 evidence). The two biggest randomized controlled studies indicated a relative risk of preterm birth of 0.58 (95% CI 0.36-0.92) and 0.55 (95% CI 0.33-0.92) in progesterone-treated groups.

This review has many strengths including good sample size and studies from wide range of duration, RCT study designs was prominent in review making study design bias minimal however, the limitations of the study includes minimal inclusion of vaginal suppository studies, also studies assessing duration of treatment and cervix dilation size should also be included.

CONCLUSION

Preterm delivery is still a serious issue in obstetric care, impacting mothers and newborns worldwide, having significant health and economic effects for the healthcare system, individuals, and families. To improve health outcomes for preterm newborns, it's important to enhance treatment for those born prematurely and establish effective prevention initiatives. Progesterone has been studied since the 1960s for its potential to lessen the incidence of premature delivery. Recent randomized trial results have renewed interest in progesterone for this indication. Randomized controlled studies and systematic reviews suggest that using progesterone may benefit certain women at high risk of preterm delivery, reducing the likelihood of birth before 34 weeks of gestation. Limited research exists on neonatal and long-term baby health outcomes, thus it's uncertain if extending pregnancy leads to better outcomes.

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CONFLICT OF INTEREST
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AUTHORS' CONTRIBUTION

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All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.