REVIEW PAPERS

Progesterone in the prevention of preterm birth – a narrative review

Progesteron w prewencji porodu przedwczesnego – przegląd literatury

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KEYWORDS:

- progesterone
- preterm birth
- cervix shortening

ABSTRACT

Preterm birth, defined as delivery before 37 weeks, stands as a leading cause of child mortality under five, necessitating effective interventions to mitigate its associated risks and complications. In 2020, 13.4 million infants were born prematurely, underscoring the global impact of this issue. Progesterone plays a vital role in preventing preterm birth by modulating various physiological mechanisms. Vaginal administration of progesterone has been demonstrated to significantly reduce preterm delivery rates and neonatal mortality among high-risk women. This review aims to assess the efficacy of vaginal progesterone in reducing preterm birth rates. Additionally, it evaluates the appropriateness of progesterone use in different pregnancy scenarios, including singleton gestations with and without prior spontaneous preterm births, as well as multiple pregnancies. Future research should aim to standardize protocols for cervical measurements and progesterone dosage to enhance clinical guidelines and improve treatment outcomes. Ultimately, these efforts are essential for advancing neonatal health and increasing survival rates worldwide. A comprehensive understanding and better implementation of these practices are crucial for achieving optimal health outcomes.

SŁOWA KLUCZOWE:

- progesteron
- poród przedwczesny
- skracanie szyjki

STRESZCZENIE

Poród przedwczesny, definiowany jako poród przed 37. tygodniem ciąży, jest główną przyczyną śmiertelności dzieci poniżej piątego roku życia i wymaga wdrożenia skutecznych działań zapobiegawczych. W 2020 roku przedwcześnie urodziło się 13,4 miliona noworodków, co podkreśla globalny charakter problemu. Progesteron odgrywa kluczową rolę w zapobieganiu porodowi przedwczesnemu w związku z jego wielokierunkowym wpływem na mechanizmy fizjologiczne. Wykazano, że podawanie progesteronu dopochwowo znacząco zmniejsza wskaźniki porodów przedwczesnych i śmiertelności noworodków wśród kobiet w ciąży wysokiego ryzyka. Niniejszy przegląd literatury ma na celu ocenę skuteczności progesteronu dopochwowego w zmniejszaniu występowania porodów przedwczesnych. Dodatkowo oceniono adekwatność stosowania progesteronu w różnych przypadkach – w tym w ciążach pojedynczych z nieobciążonym wywiadem i wcześniejszymi samoistnymi porodami przedwczesnymi w wywiadzie, a także w ciążach mnogich. Przyszłe badania powinny dążyć do standaryzacji protokołów pomiaru szyjki macicy i dawkowania progesteronu, aby poprawić wyniki leczenia. Ostatecznie te działania są niezbędne dla poprawy zdrowia noworodków i zwiększenia wskaźników ich przeżywalności na całym świecie. Kompleksowe zrozumienie i lepsze wdrożenie tych praktyk jest kluczowe w celu poprawy wyników perinatalnych.

Introduction

Preterm birth, defined as the delivery before completing 37 weeks of pregnancy, encompasses various sub-categories based on gestational age, which include extremely preterm (less than 28 weeks), very preterm (28 to less than 32 weeks), and moderate to late preterm (32 to 37 weeks), as defined by the WHO. In 2020, an alarming 13.4 million babies were born prematurely, indicating the global significance of the issue (1). The impact of preterm birth is not only prevalent worldwide but also profound with its consequences for the children. Complications arising from preterm birth constituted the leading cause of death among children under the age of five in 2019, comprising 17.7% of all child deaths and 36.1% of neonatal

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deaths (2). Nearly 900,000 children lost their lives in 2019 due to preterm birth-related complications (2). Surviving preterm neonates face further risks, due to higher susceptibility to short-term complications, long-term neurodevelopmental disabilities, chronic diseases in adulthood, and even premature mortality in early to mid-adulthood. Recognizing the severity of preterm birth complications, clinical observations have suggested that the administration of progesterone may play a crucial role in preventing prematurity. Therefore, it becomes paramount to determine the optimal timing, group of recipients, and forms of progesterone administration, to describe the risk of preterm birth and associated challenges.

Literature search ad study selection

A narrative literature review was conducted utilizing electronic databases, with MEDLINE via PubMed as the primary source. The inclusion criteria prioritized systematic reviews, meta-analyses, randomized controlled trials (RCTs), and prospective observational studies. All studies had to be peer-reviewed and written in English to be eligible for inclusion. Additionally, publications and articles for which the full text could not be accessed were excluded. The search strategy employed the following key query: progesterone AND (preterm birth OR cervix shortening). Additionally, the relevant studies identified during the review of these articles were included in the analysis.

Progesterone

Progesterone – a hormone essential in sustaining pregnancy – is initially produced by the corpus luteum and subsequently by the placenta. Its origin comes from Latin, derived from "pro" (in favor), "-gest" (gestation), and "-one" (ketone structure), signifying its role in supporting gestation. The significance of progesterone in pregnancy maintenance was underscored through seminal research conducted by Csapo et al., particularly highlighting its pivotal role during the first trimester. Csapo et al. demonstrated that the removal of luteal tissue results in a decline in progesterone concentration, consequently leading to abortion in the initial stages of pregnancy (3). This effect is, however, preventable through the replacement of progesterone.

The administration of substances that inhibit progesterone receptors, such as mifepristone, to pregnant women in the third trimester, has been observed to induce cervical ripening and often initiate the onset of labor. Progesterone's preventive role in preterm birth is multifaceted, acting through different mechanisms. Firstly, affecting myometrium and cervix by altering its coactivators and histone acetylation and thereby inhibiting myometrial contractility (4). Additionally, progesterone disrupts cortisol-mediated gene expression, particularly impacting the regulation of labor timing (5). The hormone also reduces the concentration of prostaglandins in amniotic fluid by limiting arachidonic acid availability (6). Moreover, progesterone plays a crucial role in blocking apoptosis in fetal membranes. Collectively, these mechanisms emphasize the efficacy of progesterone in averting preterm birth and maintaining the continuum of pregnancy (6). Natural progestogens can be administered either vaginally (PV – per vagina) or orally (PO – per os), whereas 17α-hydroxyprogesterone caproate (17-OHPC), a synthetic counterpart, is typically administered intramuscularly (IM). These substances have distinct physiological properties and pharmacological profiles, leading to variable indications for their use in obstetric care. A study conducted by Ruddock et al. demonstrated that progesterone effectively suppresses myometrial contractility in samples obtained during cesarean delivery. Conversely, 17-OHPC fails to produce a similar inhibitory effect and, notably, may stimulate myometrial contractility at elevated concentrations (7). In a meta-analysis conducted by Jarde et al., comprising 40 trials, it was consistently noted that vaginally administered progesterone proved to be the most effective intervention in preventing preterm birth and neonatal death among women at an overall risk of preterm birth (8).

Screening in pregnancy

Cervical length assessment is a non-invasive, accessible, and standardized method for determining the risk of preterm birth, regardless of the patient's past obstetrical history, thus making it applicable to all pregnant women. The Fetal Medicine Foundation (FMF) and the Cervical Length Education and Review (CLEAR) program have established a standardized educational initiative that certifies healthcare professionals in the accurate measurement of cervical length using a transvaginal probe. Despite the possibility of using a transabdominal probe for assessment, the transvaginal method is favored for its higher precision due to certain limitations with the abdominal approach (9). Comprehensive systematic reviews have demonstrated the feasibility and acceptability of measuring cervical length between 20-26 weeks of gestation as a method to identify approximately half of the preterm deliveries occurring before 34 weeks (10). Research conducted by Lim et al. highlighted that a cervical length (CL) of less than 25 mm shows higher sensitivity over other measurements (11). Incorporating the cervical length and any history of previous preterm births into the FMF calculator assess the risk of preterm delivery. By analyzing the information provided, the free online calculator offers an assessment of preterm birth risk, indicating probabilities for its occurrence before 28, 31, 34, or 37 weeks of gestation.

Risk Factors of Preterm Birth

The difficulty of establishing the preventive measures in the preterm birth lies in the multifaceted underpinning of its pathomechanism. Romero et al. identified various causes of preterm birth in their meta-analysis, including infection/inflammation, decidual hemorrhage, vascular disease, uterine overdistention, cervical disease, disruption of maternal-fetal tolerance, decidual senescence, immunologically mediated processes, maternal stress, and decline in progesterone action (12). Therefore, those can be recognized as a potential therapeutic targets for novel therapies. Significant improvements have been made in predicting and preventing spontaneous preterm birth after decades of clinical and basic research. The two primary predictors are a history of spontaneous preterm birth in a prior pregnancy sonographic short cervix (13).

Past history of preterm birth

The appropriate assessment of the past medical history with particular emphasis on the previous preterm births should be

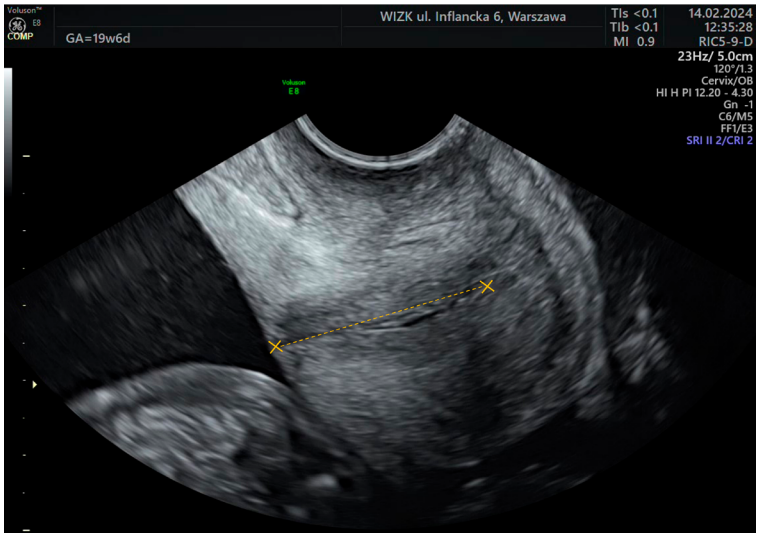

Figure 1. Ultrasound image with closed internal cervical os, length >25 mm.

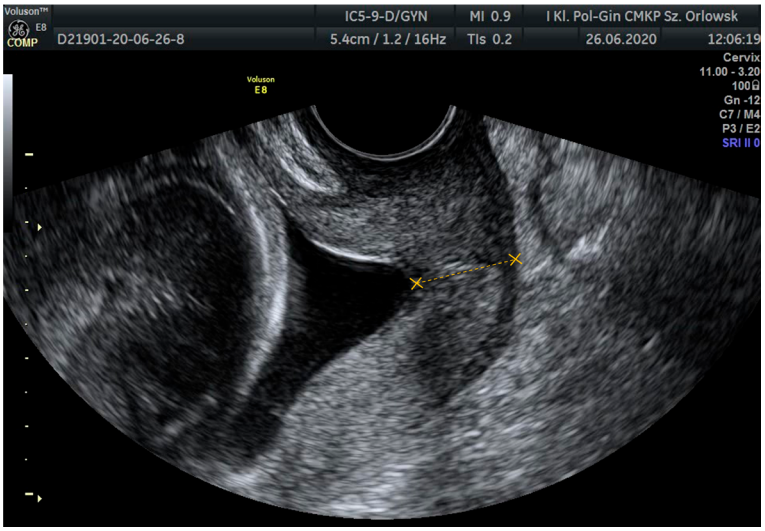

Figure 2. Ultrasound image with widened internal cervical os, V-shape, length <25 mm.

a standard in obstetrical care. Mercer et al.'s meta-analysis showed that patients with a history of spontaneous preterm birth were 2.5- to 4-times more likely to repeatedly experience it in subsequent pregnancies, emphasizing the crucial role of accurately collected obstetric histories (14). Similarly, a population-based study conducted by Rocha et al. on data from 3.5 million births found that women who experienced preterm birth in earlier pregnancies had a higher risk in subsequent pregnancies, especially if it was recurrent (15). Notably, the timing of a previous preterm birth, as indicated by Bloom's work, is of particular concern due to the frequent recurrence of miscarriages at a similar time (16). Interestingly, women born prematurely themselves face an increased risk of spontaneous preterm birth in their own pregnancies, as suggested by Porter et al. (17), possibly indicating a genetic predisposition in this entity. Besides genetic factors, environmental and behavioral risk factors may also play a major role (18).

Cervix shortening in ultrasound assessment

The current demographic trend toward an aging population and a declining birth rate results in a substantial number of women experiencing pregnancy only once in their lifetime. In these cases, relying on the history of prior deliveries becomes impractical. Consequently, the most accurate predictive factor for preterm birth in such situations is the measurement of cervical length during transvaginal ultrasound examination. This method has been proven effective in identifying women at risk of preterm birth (19). Research has demonstrated a clear correlation between midtrimester sonographic cervical length and the likelihood of preterm birth. Conventionally, the 10^{th} percentile of cervical length in the population is utilized to identify women considered "high risk" for preterm birth. At 22-24 weeks of gestation, the 10^{th} percentile corresponds to approximately 25 mm, while between 16 and 22 weeks, the 10^{th} percentile is 30 mm, coinciding with the time when women typically undergo their fetal anatomy and cervical length screening (20, 21). Investigations focusing on nulliparous women have identified a short cervix as the risk factor with the highest population risk for preterm birth (22). Despite the elevated chance of spontaneous preterm birth associated with a short cervix, it is noteworthy that a significant proportion of nulliparous women with this finding will still deliver at term (23). The method continues to be effective in both multiparous women and nulliparous women.

Vaginal progesterone in women with an asymptomatic sonographic short cervix

In 2012, Romero et al. critically examined the role of intravaginal progesterone in reducing preterm birth risks in asymptomatic women with a short cervical length in second trimester ultrasounds screening. The study, consisting of five high-quality trials including 775 women and 827 infants, addressed the effect of progesterone in lowering the likelihood of preterm delivery before 33 weeks of gestation and its impact on neonatal complications. The findings were significant, indicating a marked decrease in preterm births and associated neonatal morbidity and mortality. The treatment notably led to reduced risks of respiratory distress syndrome, lower birth weights, NICU admissions, and a decreased need for mechanical ventilation (24). Contrastingly, the 2016 Lancet-published OPTIMUM trial, which enrolled 1,228 women at risk of preterm birth, was focused on similar questions but led to different conclusions. Authors found no correlation between the use of vaginal progesterone and reductions in preterm birth or neonatal complications. Additionally, the study observed no long-term effects on the psychomotor outcomes of children at the age of two (25). Thus challenging the previous assumptions of progesterone's efficacy in such cases.

In a comprehensive effort to clarify the efficacy of vaginal progesterone for women with a short cervix, Romero revisited the question through a 2017 systematic review and meta-analysis (26). This analysis, which came after two large studies, brought together data from 974 women who participated in five trials. In the study groups, 498 were treated with vaginal progesterone, and 476 received a placebo. The analysis found that vaginal progesterone significantly lowered the rate of births happening before 33 weeks – for every 12 women treated, one premature birth was prevented (NNT = 12). It also showed that the treatment helped to extend the average time of pregnancy. Additionally, the use of vaginal progesterone led to fewer cases of RDS in newborns, less neonatal morbidity and mortality, and reduced the number of very low birthweight infants and NICU admissions. No differential efficacy was observed between dosage regimens of 90-100 mg and 200 mg per day, indicating that either could be effectively implemented in clinical practice. Furthermore, the investigation suggested no adverse impact on neurodevelopmental outcomes for children exposed to vaginal progesterone in utero up to at least 2 years of age, and possibly up to 6 years of age.

Progesterone in the prevention of preterm birth due to previous preterm deliveries

In 2018, Romero et al. found that the vaginal progesterone resulted in no difference in prevention of preterm birth in the group women with or without the history of preterm births (26). Therefore, the resulted suggested the limited effect of the vaginal progesterone as a preventive measure.

Subsequently, a randomized controlled trial from 2022 compared vaginal progesterone against a placebo or no intervention in asymptomatic women with a singleton gestation and a history of preterm birth, included a total of 2,958 women (7 smaller studies with less than 150 participants and 3 larger studies encompassing over 600 participants) (12). Patients were administered between 90 to 400 mg of progesterone vaginally, starting from weeks 20-24 up to weeks 34-36 of pregnancy. The outcomes indicated a significant reduction in preterm births before 34 and 37 weeks exclusively within the smaller study groups. In contrast, the larger study groups did not exhibit any significant reduction in preterm births or in the frequency of severe neonatal complications or the psychomotor development of children. Therefore, the current evidence does not support using vaginal progesterone to prevent preterm births or improve neonatal outcomes in women with a singleton gestation who have previously had a spontaneous preterm birth and currently show no evidence of cervical shortening in ultrasound screening (26).

Progesterone in twin pregnancy

Over the past four decades, the incidence of twin births has risen by one-third, accounting for one in every 42 babies born (27). Twin pregnancies are at a higher risk of complications for both mother and infants and up to ten times more likely to be born prematurely compared to singleton pregnancies (28). In several multicenter randomized controlled trials, the effectiveness of preventative low-dose vaginal progesterone initiated mid-gestation was examined to determine its influence on the incidence of preterm births (29). These studies presented that the intervention did not result in a significant change in outcomes. This finding was similar in the research conducted by Rehal et al., which examined the use of a higher dosage of progesterone, 600 mg per day, introduced as early as the 11th week of gestation, and similarly found no preventive benefit (30). Subsequent post hoc analysis of these findings suggested a relationship where progesterone could potentially decrease the risk of spontaneous preterm birth before 32 weeks in women with a cervical length of less than 30 mm, while also increasing the risk in those with a cervical length of 30 mm or greater. In the meta-analysis by Romero et al., the authors established that the administration of vaginal progesterone to asymptomatic women with a short cervix in the second trimester markedly decreases the likelihood of early preterm birth, neonatal death, respiratory distress syndrome, the necessity for mechanical ventilation, composite neonatal morbidity and mortality, and the incidence of birth weights below 1500 grams (31). A similar study by Jarde et al., which compared various preventative strategies for preterm birth in twin pregnancies, noted some positive secondary outcomes from vaginal progesterone but no primary prevention against preterm birth (32). Consequently, these complex outcomes indicate that routine universal administration of intravaginal progesterone as a preventative measure cannot be recommended in multiple pregnancy.

Further research has been conducted on different forms of progesterone, such as 17-alpha-hydroxyprogesterone caproate (17-OHPC) administered via intramuscular injections indicating no benefits in twin pregnancies (33). Specifically, 17-OHPC did not significantly extend the duration of pregnancy in asymptomatic women with twin pregnancies and a short cervix (34). Additionally, 17-OHPC did not prevent spontaneous preterm birth or neonatal morbidity in women with twins with history of previous premature singleton birth (35). Some studies have even expressed concerns about the use of 17-OHPC in twin pregnancies, associating its use with an earlier gestational age at the rupture of membranes or delivery in twins compared to those who did not receive 17-OHPC (34, 36).

Table 1. Overview of progesterone usage guidelines for prevention in preterm birth.

	ACOG (2023 update)	FIGO (2019)	NICE (2022 update)	SOGC (2020)	PSOG (2015)
singleton pregnancy with no previous preterm birth	Cervical length should be visualized at the time of the 18 0/7-22 6/7 weeks of gestation anatomy assessment. Vaginal progesterone is recommended for cervical length equal to or less than 25 mm. IM 17-OHPC is not indicated.	Women at high risk of preterm birth (either a previous spontaneous preterm birth and/ or sonographic short cervix) with a singleton gestation should be offered daily vaginal progesterone or weekly 17-OHPC treatment.	Consider prophylactic vaginal progesterone **if** results from a transvaginal ultrasound scan carried out between 16+0 and 24+0 weeks of pregnancy that show a cervical length of 25 mm or less.	Women with short cervical length (≤25 mm by transvaginal ultrasound between 16 and 24 weeks), vaginal progesterone in a daily dose of 200 mg is recommended.	Vaginal progesterone in a daily dose of 200 mg is recommended for cervical length equal to or less than 25 mm before 33 week of gestation. After successful tocolysis in case of preterm birth, 200-400 mg progesterone vaginally is recommended. No recommendation in case of a previous spontaneous preterm birth.
singleton pregnancy and previous spontaneous preterm birth	Serial (every 1-4 weeks) endovaginal ultrasound measurement of cervical length beginning at 16 0/7 and repeated until 24 0/7 weeks of gestation. Vaginal progesterone is considered with a cervical length less than 25 mm (**versus** cerclage) IM 17-OHPC – insufficient data.		Consider prophylactic vaginal progesterone **if only** a history of spontaneous preterm birth (up to 34+0 weeks of pregnancy) or loss (from 16+0 weeks of pregnancy onwards) **or** offer a choice of prophylactic vaginal progesterone or prophylactic cervical cerclage to women who have both 1) a history of spontaneous preterm birth, 2) results from a transvaginal ultra-sound scan carried out between 16+0 and 24+0 weeks of pregnancy that show a cervical length of 25 mm or less.	Vaginal progesterone therapy in a daily dose of 200 mg is recommended.	
multiple gestation	Cervix should be visualized at the time of the 18 0/7-22 6/7 weeks of gestation anatomy assessment. Vaginal progesterone – insufficient data. IM 17-OHPC is not indicated.	For women with unselected multiple pregnancies, progesterone therapy is not recommended. For women with multiple pregnancies and a risk factor such as previous preterm birth, it is unknown whether progesterone therapy is effective.	Vaginal progesterone is insufficient data. Do not offer intramuscular progesterone to prevent spontaneous preterm birth in women with a twin or triplet pregnancy.	With a twin pregnancy (and by extrapolation of data, with a higher-order multiple pregnancy) and with a short cervical length (≤25 mm by transvaginal ultrasound between 16 and 24 weeks), vaginal progesterone therapy is recommended.	Vaginal progesterone is insufficient data.

ACOG – The American College of Obstetricians and Gynecologists; **FIGO** – The International Federation of Gynecology and Obstetrics; **NICE** – National Institute for Health and Care Excellence; **SOGC** – Society of Obstetricians and Gynaecologists of Canada; **PSOG** – Polish Society of Obstetricians and Gynecologists.

Conclusions

Progesterone plays a multifaceted role in the prevention of preterm birth by affecting several physiological mechanisms, and when administered vaginally, it has been demonstrated as highly successful in diminishing the rates of preterm deliveries and subsequent neonatal fatalities among women considered to be at heightened risk. This is especially true when combined with transvaginal cervical length assessments, a standardized method to predict preterm birth risk, which, along with a history of spontaneous preterm birth serves as a primary predictor. Moreover, current evidence does not recommend vaginal progesterone for women with a singleton gestation who have had previous spontaneous preterm births but show no cervical shortening in the present pregnancy. Additionally, the routine, universal prophylactic use of intravaginal progesterone is not advised in cases of multiple pregnancies due to a lack of supporting research. Furthermore, recommendations lack standardized protocols regarding the timing of cervical measurements and the dosage of progesterone, highlighting areas for future research and consensus development.

Limitations

This study faces several limitations inherent to its methodology. Firstly, the narrative review approach, while comprehensive, restricts our analysis to selected literature, potentially overlooking relevant findings not covered in our review. Despite our efforts to select the most impactful studies with large, randomized participant groups, our selection process inevitably introduces a degree of subjectivity. Moreover, the interpretation of results remains personal, reflecting our understanding and perspective, which may not encompass all possible interpretations.

Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

(1) Ohuma EO, Moller AB, Bradley E, Chakwera S, Hussain-Alkhateeb L, Lewin A, et al. National, regional, and global estimates of preterm birth in 2020, with trends from 2010: a systematic analysis. The Lancet 2023; 402(10409):1261-71.

(2) Perin J, Mulick A, Yeung D, Villavicencio F, Lopez G, Strong KL, et al. Global, regional, and national causes of under-5 mortality in 2000-19: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet Child Adolesc Health 2022; 6(2):106-15.

(3) Csapo AI, Knobil E, Van Der Molen HJ, Wiest WG. Peripheral plasma progesterone levels during human pregnancy and labor. Am J Obstet Gyneco 1971; 110(5):630-2.

(4) Norwitz ER, Caughey AB. Progesterone supplementation and the prevention of preterm birth. Rev Obstet Gynecol 2011; 4(2):60-72.

(5) Karalis K, Goodwin G, Majzoub JA. Cortisol blockade of progesterone: A possible molecular mechanism involved in the initiation of human labor. Nat Med 1996; 2(5):556-60.

(6) Luo G, Abrahams VM, Tadesse S, Funai EF, Hodgson EJ, Gao J, et al. Progesterone Inhibits Basal and TNF-α-Induced Apoptosis in Fetal Membranes: A Novel Mechanism to Explain Progesterone-Mediated Prevention of Preterm Birth. Reprod Sci 2010; 17(6):532-9.

(7) Ruddock NK, Shi SQ, Jain S, Moore G, Hankins GDV, Romero R, et al. Progesterone, but not 17-alpha-hydroxyprogesterone caproate, inhibits human myometrial contractions. Am J Obstet Gynecol 2008; 199(4):391.e1-391.e7.

(8) Jarde A, Lutsiv O, Beyene J, McDonald S. Vaginal progesterone, oral progesterone, 17-OHPC, cerclage, and pessary for preventing preterm birth in at-risk singleton pregnancies: an updated systematic review and network meta-analysis. BJOG Int J Obstet Gynaecol 2019; 126(5):556-67.

(9) Creswell L, Rolnik D, Lindow S, O'Gorman N. Preterm Birth: Screening and Prediction. Int J Womens Health 2023; Volume 15:1981-97.

(10) Celik E, To M, Gajewska K, Smith GCS, Nicolaides KH. Cervical length and obstetric history predict spontaneous preterm birth: development and validation of a model to provide individualized risk assessment. Ultrasound Obstet Gynecol 2008; 31(5):549-54.

(11) Lim AC, Hegeman MA, Huis In 'T Veld MA, Opmeer BC, Bruinse HW, Mol BWJ. Cervical length measurement for the prediction of preterm birth in multiple pregnancies: a systematic review and bivariate meta-analysis. Ultrasound Obstet Gynecol 2011; 38(1):10-7.

(12) Conde-Agudelo A, Romero R. Does vaginal progesterone prevent recurrent preterm birth in women with a singleton gestation and a history of spontaneous preterm birth? Evidence from a systematic review and meta-analysis. Am J Obstet Gynecol 2022; 227(3):440-461.e2.

(13) Romero R, Dey SK, Fisher SJ. Preterm labor: One syndrome, many causes. Science 2014; 345(6198):760-5.

(14) Mercer BM, Goldenberg RL, Das A, Moawad AH, Iams JD, Meis PJ, et al. The preterm prediction study: A clinical risk assessment system. Am J Obstet Gynecol 1996; 174(6):1885-95.

(15) Rocha AS, De Cássia Ribeiro-Silva R, Paixao ES, Falcão IR, Alves FJO, Ortelan N, et al. Recurrence of preterm births: A population-based linkage with 3.5 million live births from the CIDACS Birth Cohort. Int J Gynecol Obstet 2022; 158(3):605-12.

(16) Bloom S. Recurrence of preterm birth in singleton and twin pregnancies. Obstet Gynecol 2001; 98(3):379-85.

(17) Porter T, Fraser A, Hunter C, Ward R, Varner M. The risk of preterm birth across generations. Obstet Gynecol 1997; 90(1):63-7.

(18) Mazaki-Tovi S, Romero R, Kusanovic JP, Erez O, Pineles BL, Gotsch F, et al. Recurrent Preterm Birth. Semin Perinatol 2007; 31(3):142-58.

(19) Son M, Miller ES. Predicting preterm birth: Cervical length and fetal fibronectin. Semin Perinatol 2017; 41(8):445-51.

(20) Hibbard J. Cervical length at 16-22 weeks' gestation and risk for preterm delivery. Obstet Gynecol 2000; 96(6):972-8.

(21) Iams JD, Goldenberg RL, Meis PJ, Mercer BM, Moawad A, Das A, et al. The Length of the Cervix and the Risk of Spontaneous Premature Delivery. N Engl J Med 1996; 334(9):567-73.

(22) Goldenberg RL, Iams JD, Mercer BM, Meis PJ, Moawad AH, Copper RL, et al. The preterm prediction study: the value of new vs standard risk factors in predicting early and all spontaneous preterm births. NICHD MFMU Network. Am J Public Health 1998; 88(2):233-8.

(23) Grobman WA, Lai Y, Iams JD, Reddy UM, Mercer BM, Saade G, et al. Prediction of Spontaneous Preterm Birth Among Nulliparous Women With a Short Cervix. J Ultrasound Med 2016; 35(6):1293-7.

(24) Romero R, Nicolaides K, Conde-Agudelo A, Tabor A, O'Brien JM, Cetingoz E, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. Am J Obstet Gynecol. 2012; 206(2):124.e1-124.e19.
(25) Norman JE, Marlow N, Messow CM, Shennan A, Bennett PR, Thornton S, et al. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. The Lancet 2016; 387(10033):2106-16.
(26) Romero R, Conde-Agudelo A, Da Fonseca E, O'Brien JM, Cetingoz E, Creasy GW, et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. Am J Obstet Gynecol 2018; 218(2):161-80.
(27) Monden C, Pison G, Smits J. Twin Peaks: more twinning in humans than ever before. Hum Reprod 2021; 36(6):1666-73.
(28) To MS, Fonseca EB, Molina FS, Cacho AM, Nicolaides KH. Maternal characteristics and cervical length in the prediction of spontaneous early preterm delivery in twins. Am J Obstet Gynecol 2006; 194(5):1360-5.
(29) Norman JE, Mackenzie F, Owen P, Mactier H, Hanretty K, Cooper S, et al. Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and meta-analysis. The Lancet 2009; 373(9680):2034-40.
(30) Rehal A, Benkő Z, De Paco Matallana C, Syngelaki A, Janga D, Cicero S, et al. Early vaginal progesterone versus placebo in twin pregnancies for the prevention of spontaneous preterm birth: a randomized, double-blind trial. Am J Obstet Gynecol 2021; 224(1):86.e1-86.e19.
(31) Romero R, Conde-Agudelo A, El-Refaie W, Rode L, Brizot ML, Cetingoz E, et al. Vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix: an updated meta-analysis of individual patient data. Ultrasound Obstet Gynecol 2017; 49(3):303-14.
(32) Jarde A, Lutsiv O, Park C, Barrett J, Beyene J, Saito S, et al. Preterm birth prevention in twin pregnancies with progesterone, pessary, or cerclage: a systematic review and meta-analysis. BJOG Int J Obstet Gynaecol 2017; 124(8):1163-73.
(33) Awwad J, Usta I, Ghazeeri G, Yacoub N, Succar J, Hayek S, et al. A randomised controlled double-blind clinical trial of 17-hydroxyprogesterone caproate for the prevention of preterm birth in twin gestation (PROGESTWIN): evidence for reduced neonatal morbidity. BJOG Int J Obstet Gynaecol 2015; 122(1):71-9.
(34) Senat MV, Porcher R, Winer N, Vayssière C, Deruelle P, Capelle M, et al. Prevention of preterm delivery by 17 alpha-hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial. Am J Obstet Gynecol 2013; 208(3):194.e1-194.e8.
(35) Ward A, Greenberg V, Valcarcel B, Boelig RC, Al-Kouatly HB, Berghella V. Intramuscular progesterone in women with twins and a prior singleton spontaneous preterm birth. Am J Obstet Gynecol MFM 2020; 2(3):100124.
(36) Lim AC, Schuit E, Bloemenkamp K, Bernardus RE, Duvekot JJ, Erwich JJHM, et al. 17α-Hydroxyprogesterone Caproate for the Prevention of Adverse Neonatal Outcome in Multiple Pregnancies: A Randomized Controlled Trial. Obstet Gynecol 2011; 118(3):513-20.