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Guideline No. 398: Progesterone for Prevention of Spontaneous Preterm Birth

(En français : La progestérone en prévention de l'accouchement prématuré spontané)

The English document is the original version. In the event of any discrepancy between the French and English content, the English version prevails.

This revised Clinical Practice Guideline was prepared by the authors and overseen by the Society of Obstetricians and Gynaecologists of Canada (SOGC)'s Maternal–Fetal Medicine Committee. It was reviewed by the SOGC's Family Medicine Advisory Committee and the Guideline Management and Oversight Committees and approved by the Board of Directors of the SOGC. This Clinical Practice Guideline supersedes Technical Update 202, published in January 2008.

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RECOMMENDED CHANGES IN PRACTICE

1. Prescribe vaginal progesterone for prevention of spontaneous preterm birth as it is considered safe and effective.
2. Administer vaginal progesterone in a daily dose of 200 mg for a singleton pregnancy and 400 mg for a multiple pregnancy.

This document reflects clinical and scientific consensus as of the date of publication and is subject to change. The information is not meant to dictate an exclusive course of treatment or procedure Institutions are free to amend the recommendations. The SOGC suggests, however, that they adequately document any such amendments.

Informed consent: Everyone has the right and responsibility to make informed decisions about their care together with their health care providers. In order to facilitate this, the SOGC recommends that they provide their patients with information and support that is evidence-based, culturally appropriate, and personalized.

Language and inclusivity: This document uses gendered language in order to facilitate plain language writing but is meant to be inclusive of all individuals, including those who do not identify as a woman/female. The SOGC recognizes and respects the rights of all people for whom the information in this document may apply, including but not limited to transgender, non-binary, and intersex people. The SOGC encourages health care providers to engage in respectful conversation with their patients about their gender identity and preferred gender pronouns and to apply these guidelines in a way that is sensitive to each person's needs.

3. Do not use intramuscular 17-α-hydroxy progesterone caproate because it is not as vaginal progesterone and may increase the risk of neonatal adverse outcomes.

KEY MESSAGES

1. Vaginal progesterone for prevention of preterm birth is recommended for women with a singleton pregnancy and previous spontaneous preterm birth or with a short cervical length.
2. Vaginal progesterone for prevention of preterm birth is recommended in women with a multiple pregnancy and a short cervical length.
3. Therapy should be initiated at 16–24 weeks gestation.
4. Based on risk factors, therapy can be continued up to 34–36 weeks gestation.

Abstract

Objectives: To assess the benefits and risks of progesterone therapy for women at increased risk of spontaneous preterm birth (SPB) and to make recommendations for the use of progesterone to reduce the risk of SPB and improve postnatal outcomes.

Options: To administer or withhold progesterone therapy for women deemed to be at high risk of SPB.

Outcomes: Preterm birth, neonatal morbidity and mortality, and postnatal outcomes including neurodevelopmental outcomes.

Intended Users: Maternity care providers, including midwives, family physicians, and obstetricians.

Target Population: Pregnant women at increased risk of SPB.

Evidence: Medline, PubMed, EMBASE, and the Cochrane Library were searched from inception to October 2018 for medical subject heading (MeSH) terms and keywords related to pregnancy, preterm birth, previous preterm birth, short cervix, uterine anomalies, cervical conization, neonatal morbidity and mortality, and postnatal outcomes. This document represents an abstraction of the evidence rather than a methodological review.

Validation Methods: This guideline was reviewed by the Maternal–Fetal Medicine Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC) and approved by the SOGC Board of Directors.

Benefits, Harms, and/or Costs: Therapy with progesterone significantly reduces the risk of SPB in a subpopulation of women at increased risk. Although this therapy entails a cost to the woman in addition to the discomfort associated with its use, no other adverse effects to the mother or the baby have been identified.

SUMMARY STATEMENTS (GRADE ratings in parentheses):

1. Progesterone therapy reduces the risk of spontaneous preterm birth in women at an increased risk based on history of previous spontaneous preterm birth or in women with a short cervical length (moderate).
2. There is insufficient evidence to support the use of progesterone for prevention of spontaneous preterm birth in women with a pregnancy in the absence of cervical shortening (moderate).
3. There is insufficient evidence to support the use of progesterone for prevention of spontaneous preterm birth in women with a normal cervical length and a prior conization procedure on the cervix or abnormal uterine anatomy (low).
4. Use of progesterone in women with arrested preterm labour is not associated with a reduced risk of spontaneous preterm birth or with improved postnatal outcomes (moderate).
5. Use of vaginal progesterone for prevention of spontaneous preterm birth has not been associated with an increase in congenital malformations or with a worsening of postnatal neurodevelopmental outcomes (moderate).

RECOMMENDATIONS (GRADE ratings in parentheses):

1. In women with a singleton pregnancy and a short cervical length (≤25 mm by transvaginal ultrasound between 16 and 24 weeks), vaginal progesterone therapy for prevention of spontaneous preterm birth is recommended (strong/moderate).
2. In women with a previous spontaneous preterm birth, vaginal progesterone therapy for prevention of spontaneous preterm birth is recommended (strong/moderate).
3. In women 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 for prevention of spontaneous preterm birth is recommended (strong/moderate).
4. In patients with a singleton pregnancy and a previous spontaneous preterm birth or a cervical length ≤25 mm between 16 and 24 weeks in the current pregnancy, if a cerclage is being considered, vaginal progesterone should be offered as an effective and potentially superior alternate therapy (strong/moderate).
5. In patients using progesterone for prevention of spontaneous preterm birth, additional therapies such as a cervical cerclage (with exception of a rescue cerclage for an examination-based diagnosis) or a pessary are not recommended (strong/moderate).
6. In patients at increased risk of spontaneous preterm birth due to a previous preterm birth, a short cervical length in the current pregnancy, or a multiple pregnancy, bed rest or reduced activity is not recommended (strong/moderate).
7. When indicated for prevention of spontaneous preterm birth in a singleton pregnancy, vaginal micronized progesterone in a daily dose of 200 mg is recommended (strong/moderate).
8. When indicated for prevention of spontaneous preterm birth in a multiple pregnancy, vaginal micronized progesterone in a daily dose of 400 mg is recommended (conditional [weak]/low).
9. When indicated, vaginal progesterone therapy should be initiated between 16 and 24 weeks gestation, depending on when the risked factor is identified (strong/moderate).
10. With consideration of individual patient risk factors, vaginal progesterone therapy can be continued up to 34–36 weeks gestation (strong/moderate).

INTRODUCTION

Preterm birth (delivery before 37 weeks gestation) remains a major clinical problem globally, affecting 15 million pregnancies worldwide, with an associated increase in neonatal and postnatal morbidity and mortality.[1] Prevalence in Canada increased from 6.4% of live births in 1981 to 6.6% in 1991, 7.6% in 2000, and 8.2% in 2004,[2,3] although a large proportion of this increase is related to multiple pregnancies. Spontaneous preterm birth (SPB) is a major contributor to preterm birth. There are few interventions that reduce the risk of preterm birth. In 1956, Csapo promoted the progesterone see-saw theory (i.e., high progesterone levels prevent uterine contractions and low levels facilitate contractions).[4] Progesterone is thought to be essential for maintenance of pregnancy in most mammalian species, including primates, and a drop in the level of progesterone has been associated with the onset of parturition.[5–7] Several studies have evaluated the role of progesterone in prevention of SPB in women with a high risk of preterm birth; these include women with a prior preterm birth, a multiple pregnancy, or a short cervical length. The purpose of this paper is to evaluate the findings of these studies and outline the current role for the use of progesterone for reducing the incidence of SPB and improving postnatal outcomes. See Table 1 of the online appendix for an outline of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system and Table 2 in the online appendix for a description the GRADE method for judgement and interpretation of strong and conditional [weak] recommendations.

SUMMARY STATEMENTS 1 2, 3, 4 and RECOMMENDATIONS 1 2, 3, 4, 5, 6

PREGNANCIES AT INCREASED RISK OF SPONTANEOUS PRETERM BIRTH

A network meta-analysis by Jarde et al. showed that, in pregnancies at increased risk of spontaneous preterm birth (SPB) based on prior preterm birth or a short cervical length, the use of vaginal progesterone significantly reduced the risk of preterm birth <34 weeks (odds ratio [OR] 0.43; 95% credible interval [CrI] 0.21–0.78; number needed to treat [NNT] 9), preterm birth <37 weeks (OR 0.51; 95% CrI 0.34–0.74; NNT 7) and risk of neonatal death (OR 0.41; 95% CrI 0.20–0.83; NNT 30).[8] This study also showed that intramuscular 17-α-hydroxy progesterone caproate (*17-OHPC*) reduced preterm birth only <37 weeks (OR 0.61; 95% CrI 0.39–0.92; NNT 9). In addition, progesterone (all types) significantly reduced the likelihood of neonatal intensive care unit admission (OR 0.39; 95% CrI 0.14–0.87; NNT 8).[8] Although most studies did not differentiate between preterm birth and spontaneous (as opposed to iatrogenic or indicated) preterm birth, even in the subgroup analysis for SPB <34 weeks, use of progesterone showed a benefit (OR 0.48; 95% CrI 0.27–0.85).[8] In women at increased risk of SPB, there may be a significant overlap of 2 risk factors (i.e., previous SPB and short cervical length). Andrews et al. showed that approximately 1 in 5 women with previous preterm birth had a short cervical length.[9] Romero et al. showed that about 30% of women with a short cervical length had a previous preterm birth.[10] However, in most studies, outcomes related to these 2 factors are difficult to differentiate. Notwithstanding this lack of clear delineation, the preponderance of evidence supports progesterone therapy as being effective for prevention of SPB in women with previous preterm birth or a short cervical length.[8,10]

Women with a Singleton Pregnancy and a Short Cervical length

In women with a sonographic short cervix (≤25 mm on transvaginal ultrasound assessment between 16 and 24 weeks), vaginal use of progesterone has been shown to improve outcomes. A meta-analysis by Jarde et al. showed that the use of vaginal progesterone significantly reduced preterm birth <34 weeks gestation (OR 0.45; 95% CrI 0.24–0.84; NNT 7).[8] Meta-analysis of individual patient data by Romero et al. showed that the use of vaginal progesterone significantly reduced the risk of preterm birth <33 weeks (14% vs. 22%; relative risk [RR] 0.62; 95% confidence interval [CI] 0.47–0.81; NNT 12).[10] In addition, there was a trend towards a reduction in the risk of neonatal death in addition to a significant reduction in the risk of respiratory distress syndrome, in composite neonatal morbidity and mortality, in the number of babies born with birth weights <1500 and <2500 g, and in admission to the neonatal intensive care unit (RR 0.47–0.82).

Women with Previous Spontaneous Preterm Birth

The network meta-analysis by Jarde et al. showed that in women with previous preterm birth, the use of vaginal progesterone significantly reduced preterm birth <34 weeks (OR 0.29; 95% CI 0.12–0.68; NNT 6).[8] This network meta-analysis included the data from the Crowther et al. trial, which did not show a benefit of vaginal progesterone in terms of the risk of preterm delivery or the neonatal outcomes in singleton or twin pregnancies.[11] However, this trial used a daily dose of 100 mg, as opposed to the minimum daily dose of 200 mg that was used in a larger proportion of patients included in the network meta-analysis by Jarde et al.[8] Given evidence of harm with vaginal

progesterone therapy has not been reported (with exception of vaginal discharge), the use of progesterone (at the daily dose of 200 mg) for prevention of SPB in this group, is believed to be reasonable, particularly if the previous preterm birth occurred before 34 weeks. However, it is important to ascertain whether the previous preterm birth was indeed SPB and not an iatrogenic or indicated preterm birth. In women with a previous preterm birth that was iatrogenic or indicated, an increase in the risk of SPB is not expected; therefore, use of vaginal progesterone is neither necessary or nor recommended in this subpopulation.

In Women with a Multiple Pregnancy

In women with a higher-order multiple pregnancy, a meta-analysis by Dodd et al. showed that use of progesterone was not associated with improved outcomes related to SPB.[12] In women with a twin pregnancy, a meta-analysis by Jarde et al. showed no significant impact on the risk of delivery before 34 or 37 weeks or on neonatal death.[13] There was an improvement in some of the secondary outcomes, including very low birth weight of <1500 g (RR 0.71; 95% CI 0.52−0.98), need for mechanical ventilation (RR 0.61; 95% CI 0.45−0.82), and early neonatal death (RR 0.49; 95% CI 0.33−0.73).[13] Similarly, in women with a twin pregnancy and a short cervical length (≤25 mm), vaginal progesterone did not significantly reduce the risk of delivery before 34 or 37 weeks or neonatal death, although it showed an improvement in some of the secondary outcomes, including an increase in gestational age (mean difference [MD] 1.00 weeks; 95% CI 0.36−1.64 weeks) and a reduction in the risk of very low birth weights <1500 g (RR 0.45; 95% CI 0.32−0.63), need for mechanical ventilation (RR 0.47; 95% CI 0.32−0.69), and early neonatal death (RR 0.49; 95% CI 0.33−0.73).[13] However, intramuscular progesterone (*17-OHPC*) increased the risk of some of the secondary outcomes.[13] A meta-analysis of individual patient data of randomized controlled trials (RCTs) in asymptomatic women with a twin pregnancy and a short cervical length (≤25 mm) by Romero et al. showed a significantly lower risk of preterm birth <33 weeks (31.4% vs. 43.1%; RR 0.69; 95% CI 0.51−0.93) with use of vaginal progesterone.[14] In addition, there was a significantly lower risk of neonatal death (RR 0.53; 95% CI, 0.35−0.81), respiratory distress syndrome (RR 0.70; 95% CI 0.56−0.89), and composite neonatal morbidity and mortality (RR 0.61; 95% CI 0.34−0.98).[14] In summary, there is insufficient evidence to support the use of progesterone in all multiple pregnancies. However, in women with a short cervical length, the use of vaginal progesterone appears to reduce the risk of preterm birth and adverse postnatal outcomes.

Other Indications

Progesterone has been empirically used for other conditions where the risk of SPB is increased. These include history of a conization procedure on the cervix (e.g., cold knife cone, loop electrosurgical excision) or abnormal uterine anatomy (e.g., uterine didelphys, bicornuate uterus, uterine septum, uterine fibroids).[15,16] In women with a prior conization procedure on the cervix, a short cervical length predicts an increased risk of preterm birth.[15] In the absence of specific evidence guiding management of women with cervical shortening in association with these conditions, progesterone therapy can be considered as in other women with a short cervical length. However, in the absence of cervical shortening, there is no evidence that the use of progesterone therapy is beneficial in reducing the risk of SPB in women with history of a conization procedure on the cervix or with an abnormal uterine anatomy.[10,17]

In the presence of preterm labour that subsequently arrested, 2 RCTs failed to show any benefit of progesterone in reducing the risk of SPB or an improvement in postnatal outcomes.[18,19]

Alternate/Adjunctive Therapies

In women with an increased risk of SPB, other therapies that are often considered are a cervical cerclage and a vaginal pessary. Network meta-analysis by Jarde et al. showed that, in pregnancies at increased risk of SPB based on prior preterm birth or a short cervix, the use of progesterone was more effective than the use of a cerclage or a pessary.[8] Another meta-analysis by Jarde et al. showed that a cerclage or a pessary in addition to progesterone did not improve outcomes in women at an increased risk of preterm birth.[20] An indirect comparison meta-analysis by Conde-Agudelo et al. showed a similar effectiveness of vaginal progesterone and cervical cerclage in reducing preterm birth and adverse perinatal outcomes in women with a singleton, a previous SPB, and a short cervical length.[21] Therefore, vaginal progesterone (a less invasive intervention) should be considered as an effective and potentially superior alternative to cervical cerclage (or vaginal pessary). Further, based on current evidence a cerclage or vaginal pessary does not further improve the outcomes for women on vaginal progesterone and is, therefore, not recommended. However, for patients on progesterone therapy, the aforementioned discussion does not preclude the use of a rescue cerclage for an examination-based diagnosis (i.e., an effaced or dilated cervix) as opposed to a cerclage for a shortened cervix (i.e., a therapeutic cerclage for ultrasound-based diagnosis).[22] When a prophylactic or history-indicated cerclage or a therapeutic cerclage for an

ultrasound-based diagnosis has already been performed, the use of vaginal progesterone is unlikely to provide any additional benefit.[22]

Bed rest or reduced activity has been traditionally used as an adjunct to prevention of SPB. However, there is no evidence that these measures result in a reduction in the risk of SPB in singleton or multiple pregnancies.[23–25] A recent RCT on exercise during pregnancy in women with a short cervical length showed no adverse effect and even a trend towards reduction in preterm birth rate.[26] Although avoidance of strenuous activity is reasonable, prescription of bed rest or reduced activity is unlikely to be beneficial. Further, such intervention has potential for harm that includes physical (loss or muscle and bone mass, increased risk of venous thromboembolism) as well as psychological harm.

SUMMARY STATEMENT 5

SAFETY OF USE

Use of vaginal progesterone for prevention of SPB in women with a singleton pregnancy does not have an adverse effect on neurodevelopmental outcomes.[27,28] Similarly, no significant difference in the risk of congenital malformations or neurodevelopmental abnormality was noted with use of progesterone for prevention of SPB in women with a twin pregnancy.[29,30] Therefore, there is no evidence that use of vaginal progesterone for prevention of SPB increases the risk of congenital malformations or has an adverse effect on postnatal neurodevelopmental outcomes.

RECOMMENDATIONS 7, 8

FORMULATION, ROUTE OF ADMINISTRATION, AND DOSE

Based on the preceding discussion, vaginal micronized progesterone appears to be more effective than intramuscular progesterone analogue.[8,21,31] Further, there is potential for increase in the composite adverse neonatal outcomes with the use of intramuscular progesterone.[8,31] Therefore, in patients for whom progesterone therapy for prevention of SPB is planned, use of vaginal micronized progesterone is safer and more effective than intramuscular progesterone. Absolute or relative contraindications for use can include allergy to soy or peanuts and history of thromboembolism or liver disease; refer to the product monograph for this information.

In women with a short cervical length, there was no difference in the effectiveness of vaginal progesterone for prevention of preterm birth when either 90–100 or 200 mg daily was used.[10] In women with previous SPB, the trial by Crowther et al. that used 100 mg daily did not show benefit.[11] However, the meta-analysis in which a majority of patients used at least 200 mg daily did show benefit.[8] Therefore, use of vaginal progesterone in a dose of 200 mg daily (when indicated for prevention of SPB) may be more effective. For a twin pregnancy in women with a short cervical length, an evaluation of studies presented in the meta-analysis by Romero et al. indicates the use of 400 mg daily was effective.[14] Use at bedtime may be more convenient and perhaps more effective. When a dose of 400 mg is being used, administration divided into 2 doses can be considered.

RECOMMENDATIONS 9, 10

DURATION OF USE

There is fair heterogeneity in the timing of initiation of progesterone therapy for prevention of SPB in various trials evaluating its use in women with a previous preterm birth, short cervical length, and twin pregnancies.[8,10,13,14,21] Factoring in these differences, the pathophysiology of SPB, and the need for avoidance of a complex algorithm, based on the time of identification of the risk factor(s) and the perceived risk of SPB, initiation of therapy as soon as feasible between 16 and 24 weeks gestation is felt to be reasonable in women with a previous SPB or short cervical length on transvaginal ultrasound assessment. The duration of use should be based on consideration of several factors, including potential for benefit, logistical issues (patient's proximity to a tertiary care centre), and patient's wishes, particularly related to the discomfort associated with use of the medication. Also, given the surmise that progesterone blocks the transition of the uterus from quiescence to activation phase,[4,5] with requirement of an intermediary step of progression to the stimulation phase prior to onset of labour, it is unlikely that labour will ensue immediately after stopping the treatment. Therefore, use up to 34–36 weeks gestation is felt to be reasonable. Based on individual patient factors and perceived risk of preterm delivery, discontinuation of therapy prior to 34 weeks can be considered. In women for whom progesterone is being

used periconceptually or in the first trimester for reducing the risk of miscarriage, it can be discontinued as dictated by that indication and then restarted at the appropriate dosage and gestational age when indicated for prevention of SPB.

CONCLUSION

In women with a singleton or twin pregnancy (or a higher-order multiple pregnancy, by extrapolation), in the presence of an additional risk factor (i.e., short cervical length [≤25 mm] or a previous preterm birth), the use of vaginal progesterone reduces the risk of SPB and improves postnatal outcomes. Vaginal progesterone should be considered as an alternate therapy to cervical cerclage. Addition of cervical cerclage or use of a vaginal pessary does not improve outcomes for patients receiving vaginal progesterone. Bed rest or reduced activity is not beneficial and can be potentially harmful in this population.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jogc.2019.04.012.

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