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The Use of Progesterone for Prevention of Preterm Birth

This technical update has been reviewed by the Maternal Fetal Medicine Committee and approved by the Executive of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: To introduce new information on the use of progesterone to prevent premature labour and to provide guidance to obstetrical caregivers who counsel women on the merits of this choice

Options: This discussion is limited to progesterone therapy for prevention of preterm labour (PTL) in women at increased risk of PTL.

Evidence: A search of both Medline and the Cochrane Library identified the most relevant medical evidence. This document represents an abstraction of the evidence rather than a methodological review. The level of evidence and quality of recommendations are described using the criteria and classifications of the Canadian Task Force on Preventive Health Care (Table 1).

Values: This update is the consensus of the Maternal Fetal Medicine Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC).

Benefits, Harms, and Costs: Counselling the patient at increased risk for PTL should include consideration of the potential benefits of progesterone use and our lack of/limited knowledge of many neonatal outcomes and optimal dosing.

Sponsor: Society of Obstetricians and Gynaecologists of Canada.

Recommendations

1. Women at risk for PTL should be encouraged to participate in studies on the role of progesterone in reducing the risks of preterm labour. (I-A)
2. Women should be informed about the lack of available data for many neonatal outcome variables and about the lack of comparative data on dosing and route of administration. Women with short cervix should be informed of the single large RCT showing the benefit of progesterone in preventing PTL. (I-A)
3. Women and their caregivers should be aware that a previous preterm labour and/or short cervix (< 15 mm at 22–26 weeks' gestation) on transvaginal ultrasound could be used as an indication for progesterone therapy. The therapy should be started after 20 weeks' gestation and stopped when the risk of prematurity is low. (I-A)
4. On the basis of the data from the RCTs and meta-analysis, it is recommended that in cases where the clinician and the patient have opted for the use of progesterone the following dosages should be used:
   - For prevention of PTL in women with history of previous PTL: 17 alpha- hydroxyprogesterone 250 mg IM weekly (IB) or progesterone 100 mg daily vaginally. (I-A)
   - For prevention of PTL in women with short cervix of < 15 mm detected on transvaginal uktrasound at 22–26 weeks progesterone 200 mg daily vaginally. (I-A)

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Key Words: Preterm labour, progesterone, short cervix, prematurity

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of Evidence Assessment*	Classification of Recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	I. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[30]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the The Canadian Task Force on Preventive Health Care.[30]

INTRODUCTION

Preterm birth remains a major clinical problem. Prevalence in Canada increased from 6.3% of live births in 1981–1983 to 6.6% in 1991 and 7.6% in 2000,[1,2] although a large portion of this increase is related to multiple pregnancies. There are very few interventions that improve the prognosis of preterm labour. The use of antenatal corticosteroids was shown consistently to have such an effect,[3] but most studies on tocolysis, with the exception of one recent paper on nitroglycerin,[4] had very limited clinical use. Almost 50 years ago, Csapo et al.[5] promoted the progesterone see-saw theory, which is that high progesterone levels prevent uterine contractions and low levels facilitate such contractions. This is one reason for the use of progesterone therapy in early pregnancy and the use of RU486, a progesterone antagonist, to induce abortions. It seems that the hormonal control of contractions and labour in humans is more complex than in other animals and that progesterone may have a more limited role than in animal models.[6] Recently several studies on the use of progesterone to prevent preterm labour have been published. The purpose of this paper is to evaluate the information in these studies and outline the current role for the use of progesterone for this indication.

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
CI	confidence interval
PTL	preterm labour
RCT	randomized controlled trial
RR	relative risk

DATA ON PROGESTERONE AND PRETERM LABOUR

Many studies have examined the use of progesterone for prevention of preterm labour. Mackenzie et al.[7] found 735 such studies, but only three were appropriate for inclusion in their meta-analysis on therapy in the second trimester, which showed that the use of progestins in women at risk for preterm labour reduced its occurrence by 43% (RR 0.57 [0.36–0.90]). Similar reduction of preterm births prior to 35 weeks (33%) and 32 weeks (42%) was found. Two other meta-analyses by Sanchez Ramos et al.[8] and Dodd et al.[9] were completed recently. Dodd et al. concluded that women who received progesterone were statistically significantly less likely to give birth before 37 weeks (RR 0.58; 95% CI 0.48–0.70), to have an infant with birth weight of > 2.5 kg (RR 0.62; 95% CI 0.49–0.78), or to have an infant diagnosed with intraventricular hemorrhage (RR 0.25; 95% CI 0.08–0.82). Their analysis showed no apparent benefit to early start of the progesterone administration or in the use of higher doses. Sanchez-Ramos et al. selected 10 papers for

Table 2. Study characteristics (adapted from Dodd et al.[9])

Authors/year	N	Agent	Selection criteria	Time (weeks)
LeVine 1964[10]	29	17P (500 mg/wk)	SA × 3	> 16 to 36
Papiernik 1970[11]	97	17P (250 mg q.3d)	High PTL score	28–32 × 8 doses
Johnson et al. 1975[12]	43	17P (250 mg/wk)	SA × 2 or PTL < 36 wks	Booking to 37
Hauth et al. 1983[13]	168	17P (1 g/wk)	None	16–20 to 36
Yemini et al. 1985[14]	79	17P (250 mg/wk)	SA × 2 and/or PTL × 2	Booking to 37
da Fonseca et al. 2003[15]	142	Progesterone (100 mg/d)	PTL/cerclage/uterine anomaly	24–34
Meis et al. 2003[16]	463	17P (250 mg/wk)	PTL	16–20 to 36
Fonseca et al. 2007[17]	250	Progesterone (200 mg/d)	Cx < 15mm at 22–26 wks	24–34
Rouse et al. 2007[18]	661	17P (250 mg/wk)	twins	16–20 to 36

analysis, and their results were similar to those of the two other meta-analyses. The characteristics of these studies and more recent RCTs are outlined in Table 2.

Reviews and meta-analysis on the topic published prior to 2000 differed in methodology and inclusion criteria from one another. None of them included the latest RCTs reviewed here. Daya et al.[19] looked at the use of progestins to prevent losses in women who had recurrent losses. Kierse et al.[20] limited their analysis to therapy with 17 alpha-hydroxyprogesterone, and the review by Goldstein et al.[21] included studies on women at low risk for PTL. The studies by Daya et al. and Kierse et al. (but not the study by Goldstein et al.) showed some benefit in using progesterone. Other publications on cervical length changes and PTL are supportive.[22-24]

The main results of the RCTs outlined above are provided in Tables 3 and 4.

SUMMARY OF THE CURRENTLY AVAILABLE DATA

1. Prevention of PTL

The summary of data presented above indicates that administration of progesterone in the second trimester to women with short cervix or with a previous history of preterm labour may reduce their risk for preterm birth. This modifies the sole indication of PTL outlined in the ACOG technical bulletin of 2003.[25] The ACOG guideline cautiously recommends the use of progesterone exclusively in women with previous preterm labour.

2. Frequency of Use

The frequency of progesterone use based on the ACOG recommendations increased in the US from 38% in 2003 to 67% in 2005.[26] In contrast, a recent Canadian study[27] showed that only 7% of Canadian obstetricians were using progesterone for the prevention of PTL in 2004.

3. Neonatal Outcome

The use of progesterone contributes to a significant reduction in low birth weight and intraventricular hemorrhage. Further data are needed to demonstrate a significant reduction in the following outcomes: perinatal death, respiratory distress syndrome, necrotizing enterocolitis, patent ductus arteriosus, sepsis, and retinopathy of prematurity, as the current studies and the meta-analysis are underpowered to detect effect on these parameters.

4. Safety

Progesterone has been used extensively and safely in the first trimester, when the fetus is more vulnerable for luteal phase insufficiency and recurrent losses. To date, no data from RCTs and other studies for prevention of preterm birth indicate this therapy is not safe aside from a single retrospective study[28] that showed that the incidence of gestational diabetes was 12.9% in women treated with 17P group (n = 557) compared with 4.9% in control subjects (n = 1524, $P < 0.001$; OR 2.9 [95% CI 2.1–4.1]).

5. Route of Administration and Dosage

There are no data comparing routes of administration or dosing regimens. The meta-analysis of Dodd et al.[9] did not show an added benefit of progesterone use prior to 20 weeks' gestation. A recent RCT reached the same conclusions.[29]

6. Need for Further Research

There are still large gaps in our knowledge. More data are required to properly evaluate the impact on neonatal outcomes. More information is needed on formulation (17 alpha-hydroxyprogesterone vs. progesterone), route of administration (IM vs. vaginal or oral), and the optimal dosage for progesterone use. More research is required to provide definitive data on the potential rare risks associated

Table 3. Outcomes of studies

Authors/year	RR for PTL	RR for B-weight < 2500 gm	RR for perinatal mortality
LeVine 1964[10]	0.61 (0.09–4.34)	1.62 (0.23–11.5)	3.21 (0.12–85.2)
Papiernik 1970[11]	0.18 (0.04–0.91)	0.21 (0.04–1.06)	N/A
Johnson et al. 1975[12]	0.13 (0.03–0.72)	0.39 (0.10–1.51)	0.07 (0.03–1.32)
Hauth et al. 1983[13]	0.81 (0.27–2.45)		
Yemini et al. 1985[14]	0.27 (0.09–0.85)	0.27 (0.09–0.85)	N/A
da Fonseca et al. 2003[15]	0.40 (0.17–0.94)	N/A	
Meis et al. 2003[16]	0.47 (0.31–0.69)	0.54 (0.36–0.81)	0.62 (0.27–1.40)
Fonseca et al. 2007[17]	0.56 (0.36–0.86)	0.96 (0.69–1.26)	N/A
Rouse et al. 2007[18]	1.1 (0.9–1.5)	0.9 (0.8–1.0)	1.4 (0.6 to 3.2)

Table 4. Meta-analysis of neonatal clinical outcomes from six randomized trials that compared intramuscular progesterone with placebo

Outcome	Studies (n)	Participants (n)	Relative risk 95% CI
Preterm birth (< 37 weeks)	6	878	0.59 (0.49–0.72)
Birth weight of < 2.5 kg	6	872	0.62 (0.49–0.78)
Perinatal death	6	876	0.60 (0.32–1.12)
Stillbirth	1	459	1.50 (0.31–7.34)
Neonatal death	1	459	0.44 (0.17–1.13)
Respiratory distress syndrome	2	536	0.63 (0.38–1.05)
Ventilatory support	1	454	0.59 (0.35–1.00)
Intraventricular hemorrhage	1	458	0.25 (0.08–0.82)
Necrotizing enterocolitis	1	457	Not estimable
Patent ductus arteriosus	2	535	0.55 (0.22–1.36)
Sepsis	2	536	0.96 (0.34–2.68)
Retinopathy (prematurity)	1	457	0.50 (0.15–1.70)

Used with permission from Dodd et al.[9]

with progesterone administration. Currently, there is at least one RCT (The PROGRESS study) recruiting Canadian patients at risk for PTL to evaluate vaginal administration of progesterone for prevention of PTL.

Recommendations

1. Women at risk for PTL should be encouraged to participate in studies on the role of progesterone in reducing the risks of preterm labour. (I-A)
2. Women should be informed about the lack of available data for many neonatal outcome variables and about the lack of comparative data on dosing and route of administration. Women with short cervix should be informed of the single large RCT showing the benefit of progesterone in preventing PTL. (I-A)
3. Women and their caregivers should be aware that a previous spontaneous preterm labour and/or short cervix (< 15 mm at 22–26 weeks' gestation) on transvaginal ultrasound could be used as an indication for prophylactic progesterone therapy. The therapy should be started after 20 weeks' gestation and stopped when the risk of prematurity is low. (I-A)
4. On the basis of the data from the RCTs and meta-analysis, it is recommended that in cases where the clinician and the patient have opted for the use of progesterone the following dosages should be used:
   - For prevention of PTL in women with history of previous PTL: 17 alpha-hydroxyprogesterone 250 mg IM weekly (I-B) or progesterone 100 mg daily vaginally. (I-A)
   - For prevention of PTL in women with short cervix of < 15 mm detected on transvaginal ultrasound at 22–26 weeks: progesterone 200 mg daily vaginally. (I-A)

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