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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