

Progesterone for preterm birth prevention: an evolving intervention

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Preterm birth (PTB) is the number 1 cause of neonatal morbidity and mortality, and a leading cause of long-term disability in the United States and elsewhere.^{1,2} Overall, PTB accounts for up to 12.7% of births in the developed world; the vast majority of these (~75%) occur spontaneously.^{1,3} Although secondary or tertiary interventions such as antenatal corticosteroids, postnatal surfactant, and improved neonatal care have led to reduced morbidity and mortality caused by PTB, effective primary preventive interventions have remained elusive. Encouragingly, accumulating data suggest that progesterone may be effective in preventing PTB, and the American College of Obstetricians and Gynecologists (ACOG) recognizes its use for this purpose.⁴ Nevertheless, there is still considerable uncertainty surrounding how progesterone actually works, indications for its use, and the optimal progesterone type, mode of administration, and dose. Both ACOG and the Society of Obstetricians and Gynecologists of Canada (SOGC) acknowledge the need for additional studies^{4,5} and, as of August 2008, there were > 20 registered ongoing (or planned) trials of progesterone for

We sought to review emerging data on the use of progesterone to prevent preterm birth (PTB). Using the terms “preterm or premature” and “progesterone” we queried the PubMed database, restricting our search to January 1, 2000, forward and selected randomized clinical trials (RCTs) and metaanalyses of RCTs that evaluated the use of progesterone for the prevention of PTB. We reviewed 238 abstracts and supplemented our review by a bibliographic search of selected reports. We focused on the pharmacologic aspects of progesterone and risk factor-specific outcomes. We identified a total of 17 relevant reports: 8 individual RCTs, 6 metaanalyses, and 3 national guidelines. Individual trials and metaanalyses support that synthetic intramuscular 17-alpha-hydroxyprogesterone effectively reduces the incidence of recurrent PTB in women with a history of spontaneous PTB. One trial found that vaginally administered natural progesterone reduced the risk of early PTB in women with a foreshortened cervix. The data are suggestive but inconclusive about: (1) the benefits of progesterone in the setting of arrested preterm labor; and (2) whether progesterone lowers perinatal morbidity or mortality. In some women, progesterone reduces the risk of PTB. Further study is required to identify appropriate candidates and optimal formulations.

Key words: preterm birth, prevention, progesterone

★ EDITORS' CHOICE ★

the prevention of PTB. The purpose of this report is to present a concise review of more recent data (since 2000) on progesterone use specifically for PTB prevention focusing on pharmacologic options, specific clinical indications, and expected benefits.

Materials and methods

We conducted a search of the entire PubMed database (January 2000–October 2008) using the key words “progesterone” and “preterm.” A total of 240 abstracts were reviewed to identify all relevant clinical trials or metaanalyses of clinical trials evaluating the effect of antenatal maternal use of progesterone on the risk of PTB. We then conducted a bibliographic review of the selected reports. We also reviewed national guidelines for the use of progesterone to prevent PTB. Of a total of 17 reports identified, there were 8 clinical trials,^{6–13} 6 metaanalyses,^{14–19} and 3 reports of national recommendations or guide-

lines.^{4,5,20} We abstracted relevant pharmacologic data on progesterone formulation (type, dose, route, and side effects) and pregnancy outcome by risk group under study. We applied an analytic (as opposed to a synthetic) approach to the synthesis of the data from these reports (ie, we analyzed observed similarities and/or differences without conducting additional metaanalyses). Relative risk (RR) and 95% confidence interval (CI) for pertinent outcomes were obtained either from the reports themselves or, when not available, calculated from the reported data.

Results

Among the 8 clinical trials identified,^{6–13} 1 was a subgroup analysis of another included trial.¹⁰ The characteristics of the 7 primary clinical trials and 6 metaanalyses are summarized in [Tables 1 and 2](#), respectively. In addition, we identified 3 relevant national recommendations or technical reports, 2 from ACOG and 1 from SOGC.^{4,5,20} The clinical trials were all reported between 2003 and 2008; 2 trials were not placebo controlled and,

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For Editors' Commentary,
see Table of Contents

TABLE 1

Individual clinical trials of progesterone for preventing preterm birth since 2000

Study	Design	Sample Size	Progesterone intervention	Population (indication)	Primary outcome(s)
Borna and Sahabi ⁶	RCT (no placebo)	70	400 mg vaginal suppository daily	Arrested (threatened) PTL	(1) Latency (days) (2) Recurrence of PTL
O'Brien et al ⁹	RCT (placebo controlled)	659	90 mg vaginal gel	Prior SPTB, 18-22 wk	PTB $\leq$ 32 wk
Fonseca et al ⁸	RCT (placebo controlled)	250	200 mg vaginal capsule daily until 34 wk	Short cervix $\leq$ 15 mm at 20-25 wk	Spontaneous PTB < 34 wk
Rouse et al ⁷	RCT (placebo controlled)	661	250 mg 17P IM until 35 wk	Twins at 16-20 wk	(1) PTB < 35 wk or IUFD < 35 wk
Facchinetti et al ¹¹	RCT (no placebo)	60	341 mg 17P IM twice weekly	Arrested PTL	Change in cervical length
Meis et al ¹²	RCT (placebo controlled)	463	250 mg 17P IM weekly	Prior SPTB, 16 wk	PTB < 37 wk
da Fonseca et al ¹³	RCT (placebo controlled)	142	100 mg daily vaginal suppository until 34 wk	Prior SPTB, 24 wk onward	PTB < 37 wk

IM, intramuscular; IUFD, intrauterine fetal demise; PTB, preterm birth; PTL, preterm labor; RCT, randomized clinical trial; SPTB, spontaneous preterm birth; 17P, 17-alpha-hydroxyprogesterone.

Tita. Progesterone for preterm birth prevention: an evolving intervention. Am J Obstet Gynecol 2009.

therefore, not blinded. The metaanalyses were all reported between 2005 and 2008 but included clinical trials conducted as early as the 1950s. The type and dose of

progesterone, the characteristics of the studied subjects, the nature of the study outcomes, and the corresponding results varied considerably.

Pharmacologic aspects of progesterone

The key pharmacologic aspects of progesterone in the reviewed studies are

TABLE 2

Metaanalyses of clinical trials of progesterone for preterm birth prevention since 2000

Study	No. of trials	No. of women (infants)	Progesterone intervention	Population (indication)	Primary outcome(s)
Dodd et al ¹⁹	11	2425 (3187)	Any antenatal use to prevent PTB	(1) Prior SPTB (2) Multiples (twins) (3) Short cervix (4) Threatened PTL	(1) Perinatal death (2) PTB < 34 wk (3) Neurodevelopmental handicap
Coomarasamy et al ¹⁸	9 (cumulative metaanalysis)	> 1062	Any antenatal use	(1) Risk factors for PTB excluding multiples	(1) PTB < 37 wk (2) PTB < 34 wk (3) RDS
Mackenzie et al ¹⁷	3	648	Second-trimester use	(1) Increased risk for SPTB	PTB < 37 wk
Dodd et al ¹⁶	6	988	Any antenatal use	Any pregnancy	(1) Perinatal death (2) PTB < 34 wk (3) Neurodevelopmental handicap
Dodd et al ¹⁵	7	1020	Any antenatal use	Singletons	Multiple adverse infant and maternal outcomes
Sanchez-Ramos et al ¹⁴	10	1339	Any antenatal use (placebo controlled)	Women at risk for PTB	(1) PTB < 37 wk (2) Perinatal mortality

PTB, preterm birth; PTL, preterm labor; RDS, respiratory distress syndrome; SPTB, spontaneous preterm birth.

Tita. Progesterone for preterm birth prevention: an evolving intervention. Am J Obstet Gynecol 2009.

summarized in Table 3. Two types of progesterone predominate: natural and synthetic.

Natural progesterone

Almost exclusively administered vaginally, doses of natural progesterone ranged from 90-400 mg daily, initiated variably at 18-25 weeks (Tables 2 and 3). Only 1 metaanalysis included a study with oral (micronized) progesterone, and this was among women in preterm labor.¹⁸ Compared with oral administration, vaginal progesterone bypasses hepatic first-pass effects and, therefore, has better bioavailability. Vaginal administration is virtually without side effects such as sleepiness, fatigue, and headache that can occur with oral use.^{8,9} Endometrial bioavailability after vaginal progesterone use is also reported to be higher than with the intramuscular (IM) route despite lower serum levels with the former.^{9,21} This is attributed to direct transport of progesterone from vagina to the uterus: the so-called uterine first-pass effect.²²

Synthetic progesterone (17-alpha-hydroxyprogesterone)

This synthetic progesterone was given exclusively by the IM route in variable doses (25-1000 mg) and schedules (weekly-thrice weekly). Side effects occur in the majority of patients (> 50%) but are mild and generally restricted to the injection site (injection site reaction, swelling, itching, bruising).^{7,12} Follow-up (to an average age of 4 years) of children exposed to 17-alpha-hydroxyprogesterone (17P) as fetuses in the Meis trial did not suggest any long-term harmful effects including genital anomalies or alteration of gender-specific roles.²³

Outcomes

Individual clinical trials have focused on specific populations at increased risk for PTB such as those with a history of a spontaneous PTB (SPTB) or a short cervix (Table 1). Although other risk groups such as those with presumed cervical incompetence or uterine malformations were included in 1 trial,¹³ the overwhelming majority of women had a prior SPTB and we, therefore, consid-

TABLE 3

Progesterone: pharmacologic types and protocols

Type	Route	Dose (mg)	Timing	References
Synthetic 17P	IM	250	Weekly from 16-20 wk	7,12,15,19
	IM	341	Twice weekly	11,19
	IM	250	Thrice weekly	19
	IM	500	Weekly	15
	IM	250	Every 3 days from 28 wk	15
	IM	1000	Weekly from 16 wk	15
	IM	25	Every 5 days	14
Natural progesterone	Vaginal	200	Nightly, 24-33 wk	8,19
	Vaginal	400	Daily, 18 wk to delivery	6,19
	Vaginal	100	Daily capsules to 34 wk	13
	Vaginal	90	Daily, 18 wk to delivery	9
	Oral	900-1600	Daily, from onset of PTL	18

IM, intramuscular; PTL, preterm labor; 17P, 17-alpha-hydroxyprogesterone.

Tita. Progesterone for preterm birth prevention: an evolving intervention. Am J Obstet Gynecol 2009.

ered the trial to be reflective of this latter risk group. Although some metaanalyses also stratified results by these risk factors (Tables 4 and 5), others presented summary results without regard to risk factors (Table 6).

History of SPTB

Three clinical trials^{9,12,13} and 2 metaanalyses^{17,19} evaluated the impact of prophylactic progesterone on women with a history of SPTB (Table 4). Two of 3 trials reported significant reductions in PTB on the order of 30-50%.^{12,13} Vaginal progesterone (100 mg) was used in 1 of these studies,¹³ whereas 250 mg of IM 17P was used in the other.¹² The third trial did not demonstrate a reduction in PTB with use of 90 mg of vaginal progesterone gel.⁹ Both relevant metaanalyses demonstrated significant reductions in PTB < 37 weeks and/or early PTB < 34 weeks and approximately a 30-40% reduction in low birthweight (LBW) < 2500 g.^{17,19} On average, birthweight was 475 g higher in the progesterone group.¹⁷ RR for perinatal or neonatal death and respiratory distress syndrome (RDS), although not significant, were < 1 in all reports, suggesting progesterone may be associated with reduced risks of these outcomes. In addition, the US multicenter trial of 17P found significant re-

ductions in necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH) (by 75%), and need for oxygen (by 38%)¹²; 1 metaanalysis also reported trends suggesting reductions in NEC and need for ventilator support.¹⁷

Short cervix

Two trials and 1 metaanalysis specifically evaluated the impact of progesterone on women with short cervixes (Table 5). Both clinical trials reported significant reductions in measures of early PTB.^{8,10} One trial primarily demonstrated a 45-50% reduction in early PTBs < 34 weeks among women with a foreshortened cervix who received 200 mg of vaginal progesterone.⁸ The cervical length entry criterion was ≤ 15 mm, and using this criterion, 1.7% of screened women were eligible. Furthermore, progesterone was associated with a nonsignificant reduction in a composite neonatal morbidity outcome (comprising IVH, RDS, retinopathy of prematurity, and NEC: 0.59 RR (95% CI, 0.26-1.25)).⁸ The metaanalysis included only this 1 study evaluating women with a short cervix and, therefore, presents identical results.¹⁹ The other trial,¹⁰ was not really an independent trial, but rather a subgroup analysis involving only 49 women with cervical length < 28 mm from another

TABLE 4

Selected perinatal outcomes among women with a history of spontaneous preterm birth: progesterone vs placebo

Study	PTB ^a wk: RR (95% CI)	Perinatal death RR (95% CI)	Neonatal death wk: RR (95% CI)	Mean GA (wk) ^b	RDS wk: RR (95% CI)
Dodd et al ¹⁹	< 34: 0.15 (0.04-0.64) ^c < 37: 0.68 (0.45-1.02)	0.65 (0.38-1.11)	0.44 (0.16-1.18)	n/a	0.79 (0.57-1.10)
O'Brien et al ⁹	≤ 32: 0.9 (0.52-1.56) < 37: 1.08 (0.76-1.52)	n/a	0.87 (0.29-2.60)	36.6 vs 36.6	0.91 (0.56-1.50)
Mackenzie et al ¹⁷	< 37: 0.57 (0.36-0.90) ^c	0.39 (0.07-2.24)	n/a	+1.92 (0.37-4.21) ^c	0.64 (0.39-1.07)
Meis et al ¹²	< 37: 0.66 (0.54-0.81) ^c < 32: 0.58 (0.37-0.94) ^c	0.64 (0.30-1.37)	0.44 (0.17-1.13)	n/a	0.63 (0.38-1.05)
da Fonseca et al ¹³	< 37: 0.49 (0.25-0.96) ^c	n/a	n/a	n/a	n/a

CI, confidence interval; GA, gestational age; n/a, not available; PTB, preterm birth; RDS, respiratory distress syndrome.

Except where indicated, all data represent relative risks (95% CI) that, when < 1, favor progesterone.

^a GA cut-off given; ^b Actual mean GA or difference in mean GA (95% confidence interval [CI]) for progesterone use compared with placebo or no treatment; ^c Results indicate statistical significance.

Tita. Progesterone for preterm birth prevention: an evolving intervention. *Am J Obstet Gynecol* 2009.

reviewed trial.⁹ It suggested a reduction in PTB at ≤ 32 weeks but not in overall PTB < 37 weeks among those receiving 90 mg of vaginal progesterone compared with those on placebo. Because this cervical length criterion was generated post hoc, the results of this subgroup analysis should be viewed cautiously.

Multiple pregnancies

One clinical trial⁷ and 2 metaanalyses^{16,19} reported the impact on twin pregnancy (Table 5). The relatively large clinical trial using 250 mg of IM 17P found no impact on the composite primary outcome of early PTB < 35 weeks or stillbirth, early PTB alone, or any of

several morbidities including RDS.⁷ The 2 metaanalyses together included only 2 trials (including the above) of progesterone for the prevention of PTB in multiple gestation, and found no impact on either PTB or perinatal morbidity or mortality.^{16,19} Both these studies involved IM progesterone in unselected

TABLE 5

Outcomes for progesterone vs placebo among other groups at risk for preterm birth

Study/indication	PTB ^a wk: RR (95% CI)	Mean GA (wk) ^b	Perinatal death wk: RR (95% CI)	Neonatal death wk: RR (95% CI)	RDS wk: RR (95% CI)
SHORT CERVIX					
Fonseca et al ⁸	< 34: 0.56 (0.36-0.86) ^c		0.38 (0.10-1.38)	0.29 (0.06-1.42)	0.59 (0.26-1.29)
DeFranco et al ¹⁰ (< 28 mm)	≤ 32: 0 vs 29.6% ^c	+1.7 (36.3 vs 34.6)	n/a	0 vs 3.7%	0.18 (0.02-1.31)
Dodd et al ¹⁹	< 34: 0.58 (0.38-0.87) ^c	n/a	0.38 (0.10-1.40)	0.29 (0.06-1.37)	0.59 (0.29-1.19)
MULTIPLE					
Rouse et al ⁷	< 35: 1.1 (0.9-1.4)	-0.3 (34.6 vs 34.9)	n/a	n/a	1.2 (0.8-1.6)
Dodd et al ¹⁶	< 37: 1.62 (0.81-3.25)	n/a	1.95 (0.37-10.33)	n/a	n/a
Dodd et al ¹⁹	< 37: 1.01 (0.92-1.12)		1.95 (0.37-10.33)	n/a	1.13 (0.86-1.47)
THREATENED PTB					
Borna and Sahabi ⁶	n/a	+2 (36.7 vs 34.5) ^c	n/a	n/a	0.30 (0.11-0.83) ^c
Facchinetti et al ¹¹	< 37: 0.29 (0.12-0.69) ^c	n/a	n/a	n/a	n/a
Dodd et al ¹⁹	< 37: 0.29 (0.12-0.69) ^c	n/a	n/a	n/a	0.30 (0.11-0.83) ^c

CI, confidence interval; GA, gestational age; n/a, not available; PTB, preterm birth; RDS, respiratory distress syndrome; RR, relative risk.

Except where indicated, all data represent relative risks (95% confidence interval) that, when < 1, favor progesterone.

^a GA cut-off given; ^b Difference in mean GA (respective mean GA) for progesterone use compared with placebo or no treatment; ^c Results indicate statistical significance.

Tita. Progesterone for preterm birth prevention: an evolving intervention. *Am J Obstet Gynecol* 2009.

TABLE 6

Outcomes for progesterone vs placebo for metaanalyses without stratification by risk factors for preterm birth

Study/indication	PTB ^a wk: RR (95% CI)	Perinatal death RR (95% CI)	Neonatal death wk: RR (95% CI)	Mean GA (wk)	RDS wk: RR (95% CI)
Coomarasamy et al ¹⁸	< 37: 0.42 (0.31-0.57) ^b < 34: 0.51 (0.34-0.77) ^b	n/a	n/a	n/a	0.55 (0.31-0.96) ^b
Dodd et al ¹⁶	< 37: 0.65 (0.54-0.79) ^b < 34: 0.15 (0.04-0.64) ^b	0.66 (0.37-1.19)	0.59 (0.27-1.30)	n/a	0.63 (0.38-1.05)
Dodd et al ¹⁵	< 37: 0.59 (0.49-0.72) ^b	0.60 (0.32-1.12)	0.44 (0.14-1.13)	n/a	0.63 (0.38-1.05)
Sanchez-Ramos et al ¹⁴	< 37: 0.45 (0.25-0.80) ^b	0.69 (0.38-1.26)	n/a	n/a	0.83 (0.25-2.76)

CI, confidence interval; GA, gestational age; n/a, not available; PTB, preterm birth; RDS, respiratory distress syndrome; RR, relative risk. Except where indicated, all data represent relative risks (95% confidence interval) that, when < 1, favor progesterone.

^a GA cut-off given for progesterone use compared with placebo or no treatment; ^b Results indicate statistical significance.

Tita. Progesterone for preterm birth prevention: an evolving intervention. *Am J Obstet Gynecol* 2009.

multiple pregnancies. A subgroup analysis of the positive trial of vaginal progesterone (200 mg) among women with a foreshortened cervix by the plurality of their pregnancy yielded a significant reduction in PTB < 34 weeks among singletons but a nonsignificant reduction among twins. This lack of a significant reduction in twins could be either a result of a true lack of effectiveness in this group, or alternatively, inadequate statistical power.

Arrested preterm labor

As shown in Table 5, only 2 clinical trials^{6,11} and 1 metaanalysis¹⁹ reported on the use of progesterone for arrested preterm labor. One clinical trial involved 70 women with arrested preterm labor who received vaginal progesterone (400 mg daily).⁶ The primary outcome of mean latency to delivery was significantly longer in the progesterone group by approximately 12 days (36 vs 24 days), corresponding to higher mean gestational age and birthweight at delivery of more than 2 weeks and 500 g, respectively. Progesterone also significantly reduced the risk of LBW (RR, 0.52; 95% CI, 0.28-0.98) and RDS (RR, 0.30; 95% CI, 0.11-0.83).⁶ In addition, recurrent preterm labor occurred less often in the progesterone group (35% vs 58%), as did neonatal intensive care department admission (24% vs 39%) and neonatal sepsis (5% vs 18%). The second trial involved twice-weekly administration of 341 mg of 17P (vs no treatment) to 60 women with singleton pregnancy and ar-

rested preterm labor.¹¹ PTB was significantly lower (Table 5), time to delivery nearly 10 days longer (35 vs 25 days), and mean birthweight approximately 300 g higher (3103 vs 2809 g) in the progesterone group. The difference in PTB < 35 weeks (10% vs 23%) was not statistically significant (RR, 0.43; 95% CI, 0.12-1.5) but cervical shortening was significantly attenuated among women receiving progesterone. Together with their small sample sizes the major limitation of these trials was the lack of blinding. The reviewed metaanalysis included only these 2 trials and, therefore, reflected their findings.¹⁹

Combined outcomes (without stratification by risk factors)

A total of 4 metaanalyses presented overall results without stratifying by specific risk population (Table 6).^{14-16,18} The findings revealed a consistent significant reduction in PTB and early PTB corresponding to a 40-50% reduction in LBW. Perinatal or neonatal mortality and RDS were also consistently reduced, albeit nonsignificantly. Based on the Meis trial alone, 2 metaanalyses also reported a significant 75% reduction in IVH^{15,16} and 1 reported a reduction in NEC.¹⁶ Evaluation by commencement of treatment before or after 20 weeks and by cumulative weekly dose of progesterone > 500 mg or < 500 mg (without regard to route) did not reveal any differential impact.¹⁶ Cumulative metaanalysis by progressively adding trials from the earliest to the more recent

showed significant reductions in birth < 37 weeks as early as 1975.¹⁸ This latter metaanalysis was limited by the inclusion of data on women who received progesterone for habitual abortion.¹⁸

National recommendation/guidelines

We reviewed 3 reports providing recommendations or guidelines from both ACOG and SOGC.^{4,5,20} ACOG recommends that progesterone supplementation be offered to women with a prior SPTB to prevent recurrent PTB.⁴ ACOG has just reaffirmed this position specifically for women with a current singleton pregnancy, and further recommends that progesterone may be considered for women with an incidentally discovered shortened cervix (< 15 mm) but recommends against routine ultrasonographic screening to identify a shortened cervix.²⁰ The SOGC recommends further clinical trials of progesterone for all women at risk for PTB.⁵ However, they also recommend that women with a prior SPTB or with a short cervix (< 15 mm) be counseled and offered progesterone supplementation if desired. Both organizations recognize the need for further studies to determine the optimal dose and route of progesterone, and the impact of progesterone on perinatal morbidity and mortality.

Conclusions

Taken together, the reviewed data strongly suggest that prophylactic use of progesterone leads to significant reductions in measures of PTB and LBW. The

data also suggest, but less conclusively, that progesterone may confer neonatal morbidity and mortality benefit. However, the benefit of progesterone may vary by risk group, route of administration, and dose. Therefore, additional research is needed to clarify these issues. For now, when progesterone is used for PTB prevention, the following approach would appear rational based on the available data: (1) for women with a prior SPTB, weekly IM 17P (250 mg) initiated at 16-20 weeks, or daily vaginal progesterone (at least 100 mg) beginning before week 24 should be given; (2) for women with a short cervix (≤ 15 mm), 200 mg of vaginal progesterone suppositories may be reasonable, although only 1 properly conducted and analyzed trial supports such an approach; (3) for women with a twin pregnancy, progesterone is not routinely indicated, although its use may be prudent in the specific scenarios of a prior SPTB (250 mg 17P IM) or significantly (≤ 15 mm) foreshortened cervix (200 mg suppository vaginally); and (4) for women with arrested preterm labor, progesterone (400 mg daily vaginal suppository or 341 mg 17P IM twice weekly) may be considered but the available data are seriously limited by lack of blinding. It is encouraging that there are multiple ongoing trials that should further clarify the role of progesterone in PTB prevention. ■

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