Progestagens for preventing preterm birth

F. Facchinetti, V. Vaccaro, E. Annessi, G. Dante

Mother-Infant Department, Unit of Obstetrics, University of Modena and Reggio Emilia, Italy

Correspondence at: fabio.facchinetti@unimore.it

Abstract

The term "progestagens" covers a group of molecules including both the natural female sex hormones Progesterone and 17-hydroxy Progesterone as well as several synthetic forms, all displaying the ability to bind Progesterone receptors. Several studies have used Progesterone and related steroids in an attempt to prevent spontaneous preterm birth (PTB).

The present paper aims to provide a comprehensive review of the literature on the effects of progestagens effects in preventing spontaneous PTB. We consider only the information derived from randomized controlled trials (RCTs). Results are reported in 4 sections according to the clinical risk factor: 1- history of preterm delivery, 2- short cervix, either symptomatic or asymptomatic, 3- multiple pregnancies, 4- threatened preterm labour.

For the clinicians, the back home message is that a) 17 OH Progesterone caproate (17OHPc) is able to prevent PTB in women at risk because of their obstetric history, and b) vaginal Progesterone prevents PTB in women with an asymptomatic short cervix. The conclusion that progestagens are useless in multiple gestations has recently been challenged by an individual participant data (IPD) meta-analysis. No firm indications on the use of progestagens for PTB prophylaxis in women presenting with other risk factors such as symptomatic short cervix or threatened preterm labour could be found with the available data.

Key words: **Progestagens, Progesterone, 17 α OH Progesterone, 17 α OH Progesterone Caproate, preterm labour, preterm birth.**

Introduction

The syndromic nature of spontaneous preterm labour was a concept first proposed in 1994 (Romero et al., 1994). In 2009, Romero et al., have reinforced that preterm parturition should not be considered a monolithic entity, but rather a syndrome. The term ''syndrome'' is defined in the Oxford Medical Dictionary as ''a combination of symptoms and signs that form a distinct clinical picture indicative of a particular disorder''. The following mechanisms of disease have been implicated: 1) intrauterine infection/inflammation; 2) uterine ischemia; 3) uterine over-distension; 4) abnormal allogenic recognition; 5) allergic-like reaction; 6) cervical disease; and 7) endocrine disorders. This view controverts the concept that preterm parturition is simply "labor before its time" and that all causes of preterm labor are the same. The implicit consequence that preterm parturition is a syndrome with multiple etiologies is that there would not be a single treatment, diagnostic method or preventive strategy that will work for all preterm births.

So the 'cause' of preterm labour is multifactorial in origin, and it is important to consider the role of any identifiable risk factor in a woman's pregnancy.

The knowledge that an increased activity of endogenous Progesterone was a necessary event for the development and the maintenance of pregnancy dates back to the first half of the last century. Around the 60s the idea was acquired that a withdrawal of endogenous Progesterone was related to the onset of labour, even preterm. Since then, Progesterone and related synthetic compounds such as 17OHPc as well as other progestagens have been tested in clinical trials to prevent the challenging phenomenon

of PTB (Romero et al., 1994). In one of the first meta-analyses ever published about perinatal interventions, it was demonstrated that 17OHPc treatment was associated with a reduced rate of PTB in respect with placebo or no intervention. Surprisingly, such achievement was not implemented into clinical practice, nor did scientific societies endorse such conclusions producing recommendations. The Williams Obstetrics textbook 21st edition released in 2001 did not even mention Progesterone among interventions to prevent PTB (Cunningham, 2001). Clinical and experimental studies re-started in the year 2000. Now, an almost equal number of RCTs and meta-analyses are available while several trials are still being planned or are ongoing. In such clinical trials Progesterone has been administered through daily vaginal route by using both 8% gel and 100-400 micronized hormones. On the other hand, 17OHPc has been administered through IM injections, by using doses ranging from 250 to 682 mg/week, with drug dissolved in castor or ethyl oil. Given the different biological actions of Progesterone and 17OHPc, considering that we still ignore the mechanism of action of such treatments, given the heterogeneity of the inclusion criteria utilized in the different studies, it seems difficult at present to put together the results of all these RCTs under the umbrella of "progesterone treatment" (Facchinetti et al., 2009; Di Renzo et al., 2011). Maternal safety of either micronized Progesterone or 17OHPc administration has been reported in different trials. Neonatal safety has been evaluated in only one trial where mothers have been treated with 17OHPc. No effects on general health status, external genitalia and psychomotor development have been reported at follow-up. However, there is concern about the increase in fetal death in mid-trimester and the higher incidence of gestational diabetes linked to 17OHPc (Di Renzo et al., 2011).

Methods

Literature searches were performed in the following electronic databases: Medline and The Cochrane Library. We performed a search over the period January 1975 to June 2012 and only RCTs were included.

We performed a search about progestagens, their applications and potential effects for preventing PTB. Results are subdivided into 4 sections according to the clinical presentation of subject. Effects of progestagens were evaluated in (1) women with history of preterm delivery, (2) patients with short cervix, (3) women with multiple pregnancies and (4) patients with symptoms of threatened preterm labour.

Results

History of preterm delivery

The most significant and consistently identified risk factor for PTB is a woman's history of previous PTB. Data suggests the rate of recurrent PTB in this group of women to be 22.5%, a 2.5 times increased risk ratio when compared with women without previous spontaneous PTB (Mercer et al., 1999; Facchinetti and Vaccaro, 2009). For women with a history of a single PTB, the recurrence risk in a subsequent pregnancy is approximately 15%, increasing to 32% where there have been two previous PTBs (Carr-Hill and Hall, 1985). Information derived from population-based cohort data suggests that for women who give birth between 20 and 31 weeks' gestation in one pregnancy, 29.3% will give birth prior to 37 weeks in a subsequent pregnancy (Adams et al., 2000). For approximately 10% of these women, the PTB will occur at a similar gestational age (Adams et al., 2000; Kistka et al., 2007). In up to 50% of cases of PTB, the cause is spontaneous onset of labour or preterm premature rupture of membranes (pPROM) (McLaughlin et al., 2002). The obstetric history is an important predictor of spontaneous preterm delivery both in singleton and twin gestations, in particular previous spontaneous preterm delivery and late miscarriage.

In a Cochrane review, Dodd et al. (2012) included 11 RCTs (2714 women and 3452 infants) and concluded that, for women with a past history of spontaneous PTB, progestagens are associated with a statistically significant reduction in the risk of PTB less than 34 weeks' gestation (142 women; risk ratio (RR) = 0.15; 95% confidence interval (CI) 0.04 to 0.64) (one study - da Fonseca et al., 2003). Progestagens are associated with a statistically significant reduction for PTB less than 37 weeks' gestation (four studies -1255 women; RR 0.80; 95% CI 0.70 to 0.92) and infant birth weight less than 2500 grams (two studies - 501 infants; RR 0.64; 95% CI 0.49 to 0.83) (Dodd et al., 2012).

After the Cochrane review publication, Berghella et al. (2010) published a planned secondary analysis of the NICHD-sponsored trial evaluating cerclage in women with singleton gestation, a history of PTB and a ultrasound-measured short cervix. In 152 women, without cerclage, 17OHPc failed to prevent PTB < 35 weeks (the main outcome) in respect with placebo. However, the intervention group reported significantly less PTB < 24 weeks and a trend toward less perinatal death when compared to placebo.

Patients with a short cervix

Other characteristics of pregnant women are associated with an increased risk for PTB. These include women with a short cervix identified by ultrasound assessment, the presence of fetal fibronectin in the vaginal secretions, and other symptoms or signs of threatened preterm labour (Goldenberg et al., 1996; Berghella et al., 2005).

The cervix has a crucial role in the etiology of PTB, as well as in its potential prevention strategies. The identification of a short cervix on ultrasound examination (the cut off is 25 mm) has been associated with a likelihood ratio of PTB before 34 weeks' gestation of 6.29 (95% confidence interval (CI) 3.29 to 12.02) (Honest et al., 2002). The likelihood ratio of PTB before 34 weeks associated with a negative ultrasound test result was 0.79 (95% CI 0.65 to 0.95). The risk for spontaneous PTB in both singleton and twin pregnancies is inversely correlated with the cervical length: the shorter the cervix the higher the risk of preterm delivery.

The cervix is composed by 80-85% connective tissue, with collagen type 1 making up 70% of whole collagen. Cervical ripening has been hypothesized as the effect of a local activation of diverse biochemical pathways sharing those of an aseptic, pro-inflammatory reaction. The increased secretion of interleukins and nitric oxide in cervical fluids has been reported to be associated with PTB. Such mediators ultimately stimulate apoptosis, activation of proteases and disaggregation of collagen fibrils allowing cervical shortening (Lockwood et al., 1994; Facchinetti and Vaccaro, 2009).

It has been suggested before that progesterone-active compounds showed immunosuppressive effects. Indeed, Progesterone receptors were found on lymphocytes and the activation of such receptors interferes with interleukins secretion through the progesterone-induced blocking factor. In human decidual cells, *in vitro* medroxyprogesterone acetate (MPA) was able to block both IL-1β and thrombin-induced release of IL-11, a cytokine which is over-expressed in samples of decidua collected from patients undergoing a PTB associated to intrauterine infection. Moreover, in a mouse model of inflammation-induced PTB, both MPA and 17OHPc pre-treatment protected animals from PTB.

Recently, the pivotal role of IL-1β in accounting for PTB was highlighted in an experiment done in non-human primates. Pregnant animals received amniotic fluid injection of the pro-inflammatory cytokines. While IL-6 and IL-8 were rather ineffective, IL-1β injection induced preterm delivery within a few days.

In humans, IL-1β levels have consistently been found elevated in cervico-vaginal and/or cervical fluids, thus predicting those women destined to undergo spontaneous PTB. IL-1β is an early marker of host-response to infection and seems to play a main role in host reaction, more particular in cases where PTB is associated with amniotic fluid infection. IL-1β initiates a cascade of paracrine events activating several cytokines. The observation that 17OHPc induce a selective inhibition of cervical IL-1β is a key phenomenon and possibly has a pivotal role in mediating the protective effect on PTB (MacIntyre et al., 2012).

In the Cochrane review from Dodd et al. (2012) progestagens were associated with a statistically significant reduction in the risk of PTB less than 34 weeks (one study - 250 women; RR 0.58; 95% CI 0.38 to 0.87) and neonatal sepsis (one study - 274 infants; RR 0.28; 95% CI 0.08 to 0.97) when compared to placebo in women with a short cervix.

In a RCT of 17OHPc treatment for PTB prevention in nulliparous women with cervical length (CL) less than 30 mm, the frequency of PTB did not differ between the drug and placebo groups (25.1% vs. 24.2%) (Grobman, 2012). There was also no difference in delivery < 35 weeks (13.5% vs 16.1%, $p = 0,35$) or < 32 weeks (8.6% vs. 9.7%, $p = 0,61$). Although the power to show a difference was limited due to sample size, subgroup analyses also failed to demonstrate benefit from 17OHPc in women with a CL < 15 mm. According to this study, weekly IM injection of 17OHPc does not reduce the frequency of PTB in nulliparous women with a short cervix < 30 mm.

Two large RCTs on vaginal Progesterone are available. In the first one published by Fonseca et al. (2007), CL was measured by transvaginal ultrasonography at a median of 22 weeks of gestation in 24,620 pregnant women seen for routine antenatal care. CL was 15 mm or less in 413 women (1.7%) and 250 (60.5%) of them were randomly assigned to receive vaginal Progesterone (200 mg each night) or placebo from 24 to 34 weeks of gestation. Spontaneous PTB before 34 weeks of gestation was less frequent in the vaginal Progesterone group than in placebo group (19.2% vs. 34.4%; RR, 0.56; 95% CI, 0.36 to 0.86). Vaginal Progesterone was associated with a non-significant reduction in neonatal morbidity (8.1% vs. 13.8%; RR, 0.59; 95% CI, 0.26 to 1.25; P = 0.17).

The other RCT by Hassan et al. (2011) was a multicenter, randomized, double-blind, placebo-controlled trial that enrolled asymptomatic women with a singleton pregnancy and a sonographic short cervix (10–20 mm) at 19 + 0 to 23 + 6 weeks of gestation. Women were allocated randomly to receive vaginal Progesterone gel or placebo starting from 20 to 23 +

6 weeks until 36 + 6 weeks, or until rupture of membranes or delivery, whichever occurred first. Out of 465 randomized women, seven were lost to follow-up and 458 were included in the analysis. Women allocated to receive vaginal Progesterone gel (90 mg) had a lower rate of PTB before 33 weeks than did those allocated to placebo (8.9% vs 16.1%; RR, 0.55; 95% CI, 0.33–0.92). Vaginal Progesterone was also associated with a significant reduction in the rate of PTB before 28 weeks (5.1% vs. 10.3%, p = 0.04) and 35 weeks (14.5% vs. 23.3%, p = 0.02). Progesterone was also effective on neonatal outcomes such as respiratory distress syndrome (3.0% vs. 7.6%, p = 0.03), any neonatal morbidity or mortality event (7.7% vs. 13.5%, p = 0.04) and a birth weight < 1500 g (6.4% vs. 13.6%, p = 0.01). There were no differences in the incidence of treatment-related adverse events between the groups.

Women with multiple pregnancies

Multiple pregnancies contribute disproportionately to PTB. Overall, 52.2% of multiple births deliver before 37 weeks and 10.7% before 32 weeks (Stock et al., 2010). In the United States, the rate of PTB and very PTB among triplets shows a 92% and 36% increase respectively (Grobman, 2012). In the USA, 57% of twins are born with low birth weight, compared to 6% of singletons (Combs et al., 2011). The mechanisms of PTB may be different to those operating in women with a singleton pregnancy. Preterm premature rupture of membranes (pPROM) is more prevalent in twin gestations and is a major contributor to PTB (Sela and Simpson, 2011).

As yet, no treatments have been identified that can prevent PTB in multiple pregnancy. Six RCTs of progestagens to prevent PTB in twin pregnancies have now been published i.e. (Fonseca et al., 2007; Rouse et al., 2007; Briery et al., 2009; Cetingoz et al., 2011; Norman et al., 2009; Combs et al., 2011).

These studies randomized women to either 17OHPc or vaginal Progesterone pessary, and placebo. In one study, which included 67 women with twin pregnancies, 100 mg of vaginal Progesterone was found to reduce delivery before 37 weeks gestation (OR 3.48 [1.2-10.5]) (Cetingoz et al., 2011). In all the remnant studies treatment with 17OHPc or vaginal Progesterone did not lead to any significant reduction in PTB or fetal loss. In the two largest trials, however, a non-significant increase in intrauterine death was seen in the treatment group (Rouse et al., 2007; Norman et al., 2009). Furthermore, a significant difference in median gestational age favoring placebo was found in the other large trial (Combs et al., 2011).

We are aware of five other trials of progestagens in multiple pregnancies that are nearing completion or publication. In total these trials have included 3,522 women and more than 7,000 infants. An ongoing individual participant data (IPD) meta-analysis of randomized trials is combining data from these high-quality clinical trials in order to provide valuable information regarding the benefits and potential harms of progestagens. The primary outcome is adverse perinatal outcome i.e. a composite measure of perinatal mortality and significant neonatal morbidity.

In the only published meta-analysis, Romero et al. (2012) have shown that among twin gestations the administration of Progesterone did not significantly reduce the risk of PTB < 33 weeks of pregnancy (RR, 0.70; 95% CI, 0.34 –1.44). However, the intervention significantly decreased the risk of composite neonatal morbidity and mortality (RR, 0.52; 95% CI, 0.29–0.93). There were no significant differences in other outcome measures among the vaginal Progesterone and placebo groups. Moreover in the subgroup of women with a twin gestation and a short cervix, Romero et al. (2012) found that vaginal Progesterone reduces the rate of PTB at < 33 weeks by 30% and significantly reduces the composite neonatal morbidity/mortality of twins. A confirmatory study using available progestagens is urgently needed to confirm these data since a negative effect was found by the Netherlands network: 671 women with multiple gestations were randomized and intervention did not affect the rate of adverse composite neonatal outcome when compared to placebo (Lim et al., 2011).

Patients with symptoms of threatened preterm labour

In a woman's current pregnancy another characteristic that may place her at increased risk of PTB, is a threatened preterm labour. However, symptoms of preterm labour are often aspecific, i.e. Women with preterm contraction and modified cervix deliver before 37 weeks in 10-40% of the cases (Dodd et al., 2012). The question whether 17OHPc treatment affects changes in cervical length was studied in a single centre, randomised, prospective study including women with singleton pregnancy, between 25 and 33 + 6 weeks and hospitalized for preterm labour (Facchinetti et al., 2007). Sixty undelivered patients after tocolysis were randomly allocated to either observation or to receive 341 mg of 17OHPc IM twice/week, until 36 weeks of gestation. CL was measured by transvaginal ultrasound at discharge, and at day 7 and day 21 post discharge. Shortening of the cervix in the observation group was higher than in the 17OHPc group, both at day 7 (2.37 ± 2.0

Table 1. — Effects of progestagens in reducing preterm birth (PTB = preterm birth, IPD = individual patient data).

PROGESTAGEN RISK FACTOR	17 α Hydroxy Progesterone Caproate	Vaginal P suppository	Vaginal P gel
History (At least one previous spontaneous PTB)	**PREVENTS PTB** 2 RCTs (250 mg/weekly) (Johnson, 1975; Meis 2003)	**PREVENTS PTB** 1 RCT (100 mg/day) (da Fonseca, 2003)	**INEFFECTIVE** 1 RCT (90 mg/day) (O'Brien, 2007)
Hystory plus short cervix	**PREVENTS Previable Birth** 1 RCT (250 mg/weekly) (Berghella, 2010)		
Short cervix - Asymptomatic	**INEFFECTIVE** 1 RCT (250 mg/weekly) (Grobman, 2012)	**PREVENTS PTB** 1 RCT (200 mg/day) (Fonseca, 2007)	**PREVENTS PTB** 1 RCT (90 mg/day) (Hassan, 2011)
		PREVENTS PTB 1 IPD (Romero, 2012)	
Short cervix - Symptomatic	**PREVENTS PTB** 1 RCT (open) (341 mg/twice week) (Facchinetti, 2007)		-
	INEFFECTIVE 1 RCT (open) (500 mg/twice week) (Rozenberg, 2012)	**DELAY PARTURITION** 1 RCT (open) (400 mg/day) (Borna, 2008)	-
Multiple Pregnancy	**INEFFECTIVE** 3 RCTs (250 mg/weekly) (Rouse, 2007; Combs, 2011; Lim, 2011)	-	**INEFFECTIVE** 1 RCT (Norman, 2009)
Multiple Pregnancy plus short cervix		**INEFFECTIVE** (REDUCES COMPOSITE NEONATAL MORBIDITY/MORTALITY) 1 IPD (Romero, 2012)	

vs. 0.83 ± 1.74 mm, p = 0.002) and day 21 (4.60 ± 2.73 vs. 2.40 ± 2.46 mm, p = 0.002). Treatment with 17OHPc was associated with both a reduction in the risk of cervical shortening ≥ 4 mm (OR: 0.18; 95% C.I.: 0.04-0.66) and in the risk of PTB (OR: 0.15; 95% C.I.: 0.04-0.58) (Facchinetti et al., 2007).

An open-label, multi-centre, RCT included 184 women with singleton pregnancies and short cervix (cervical length less than 25 mm) admitted at 24-31 weeks' gestation for preterm labour successfully arrested by tocolytic treatment (Rozenberg et al., 2012). Randomization assigned them to receive (or not) 500 mg of i.m. 17OHPc after tocolysis ended, repeated semi-weekly until 36 weeks or PTB. The primary outcome was the time from randomization to delivery. The 17OHPc and control groups did not differ significantly for median time to delivery (64 [42–79] and 67 [46–83] days, respectively) or rates of delivery before 37, 34, or 32 weeks of gestation or adverse perinatal outcomes. According to this study, biweekly injections of 17OHPc did not significantly prolong pregnancy. In this study the latency from randomization to delivery was much longer than in other trials. Such difference is probably due to inclusion criteria, which selected a population with less severe threatened preterm labour (Rozenberg et al., 2012).

Another single centre, randomized study performed in Australia including 70 women, demonstrated that vaginal Progesterone (400 mg daily) was associated with a PTB < 37 weeks reduction (OR = 0.52; CI95%: 028-0.98) (Borna and Sahabi, 2008).

A recent controlled trial also involving a single centre was performed in 70 women presenting with

symptoms of threatened preterm labour. After the arrest of uterine activity with Magnesium Sulphate they were randomized to vaginal Progesterone (400 mg daily until delivery) or no treatment. The use of vaginal Progesterone was associated with a longer latency preceding delivery, although no figures on PTB rate were reported (Saleh Gargari et al., 2012).

Conclusion

The knowledge about the clinical use of progestagens is expanding very rapidly, as witnessed by the number of studies published during the last year. Moreover, not less than 10 RCTs are ongoing according to their registration at clinicaltrials.gov website. Such an increased interest on hormone intervention in the prevention of PTB is so dynamic that one cannot write firm conclusions.

Anyway, at present, the clinical evidences of progestagens efficacy are summarised in Table 1. According to the listed risk factors, either Progesterone or 17OHPc seem to be useful, in definite circumstances. However, it has to be underlined that the number of trials supporting or disconfirming progestagens efficacy is limited and included only a few hundreds of women.

For the clinicians, the back home message is that a) 17OHPc is able to prevent PTB in women at risk because of their obstetric history, and b) vaginal Progesterone prevents PTB in women with an asymptomatic short cervix. The conclusion that progestagens are useless in multiple gestations reached by several trials has recently been challenged by an IPD meta-analyses. Romero et al. (2012) found a reduction in the risk of composite neonatal mortality/morbidity.

Furthermore, no firm indications on the use of progestagens for PTB prophylaxis in women presenting with other risk factors (symptomatic short cervix, threatened preterm labour) could be reached with the available data.

The policy to universally screen asymptomatic women at their morphological ultrasound examination, detecting those who are risk for short cervix for treating them with progestagens is actually debated (Romero et al., 2012). Interestingly, a cost-effectiveness analysis of such policy is ongoing in the Netherlands (van Os et al., 2011).

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