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Progesterone Treatment to Prevent Preterm Birth

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Abstract

The publication in 2003 of two large randomised trials of progesterone therapy to prevent preterm delivery has generated renewed interest in this treatment and has added substantial numbers of subjects to previously published small trials. The randomised trials of progestogens have generally shown efficacy in reducing the rate of recurrent preterm delivery in women with singleton pregnancies who were at high risk for preterm labour and delivery. Most of the successful trials have employed 17α-hydroxyprogesterone caproate, and one trial has reported positive results using progesterone vaginal suppositories.

The administration of 17α-hydroxyprogesterone caproate or progesterone suppositories to women with these high-risk pregnancies showed a significant protective effect for preterm birth in six of the seven published trials. No successful trials of progestogens have been reported for women at risk for preterm delivery because of multiple gestations. Trials of progestogens after the occurrence of symptoms of labour have shown them to be ineffective in prolonging pregnancy.

Progesterone treatment for preventing preterm birth has been the subject of several relatively small trials beginning in the 1960s. Despite generally positive results from these trials, treatment with progestogens has not become widely used in the care of women at risk for preterm delivery. Recently, two large trials have reported success of progestogens in preventing recurrent preterm delivery in women at risk. The publication of these trials, one of progesterone suppositories[1] and one of 17α-hydroxyprogesterone caproate,[2] has rekindled interest in a treatment that had fallen into disuse. Thus, it is timely to review the available evidence concerning various progestogens used to prevent preterm labour and delivery.

To identify relevant published trials for this review, a computer search of PubMed was performed using the terms 'preterm birth' and 'progesterone', yielding 150 published papers from 1965 to the present.

1. The Problem of Preterm Birth

Preterm birth – delivery before 37 completed weeks of gestation – is the major determinant of infant mortality in developed countries.[3] The rate of preterm birth is greater in the US than in most developed countries and is the factor most responsible for the relatively high rate of infant mortality in the US.[3] In addition, the rate of preterm birth in the US has increased progressively over the past two decades, from 9% to 12% of all births.[4] Many attempts have been made to find a way to reduce the incidence of preterm birth. Beginning in the 1970s, drug therapy for the prevention of preterm delivery has focused mostly on the use of tocolytic drugs, to halt preterm labour after it has begun. Although trials of tocolytic drugs have shown effectiveness in halting labour for up to several days, the use of these drugs has not reduced the incidence of preterm delivery and has not shown any improvement in perinatal outcome.[5] Cervical cerclage has long been employed for women thought to have a weakness of cervical integrity, but randomised controlled trials of cervical cerclage have generally not shown effectiveness.[6] Although vaginal infections are known to be associated with an increased risk of preterm delivery, the largest and best controlled trials have found no improvement in preterm birth results from screening and treating vaginal infections.[7,8] Despite many trials of reduced physical activity, the use of tocolytic drugs to halt labour, antibacterial therapy and other strategies, no effective and reproducible method of preventing preterm birth has been demonstrated.[9] Thus, the enigma of preterm birth is widely considered to be the greatest problem in obstetrics in the developed world.

2. Actions of Progesterone

Progesterone produced by secretion from the corpus luteum and the placenta is known to be essential to the maintenance of pregnancy early in gestation.[10,11] In addition, progesterone has actions that maintain pregnancy later in gestation. Progesterone acts to relax smooth muscle in many organs, including the pregnant uterus. Progesterone has immunosuppressive activity against the activation of T lymphocytes, and blocks the effects of oxytocin on myometrium.[11,12] Perhaps most importantly, progesterone is a potent inhibitor of the formation of gap junctions between myometrial cells.[13] These intercellular communications are essential for the propagation of coordinated uterine muscle activity leading to labour.

In addition to actions of progesterone for general maintenance of pregnancy, evidence exists from data obtained from both animal and human studies that changes in local or systemic levels of progesterone may play a role in the initiation of labour.

The importance of progesterone in regulating the onset of labour is supported by the observation that in sheep, goats and many other mammalian species, a decrease in plasma progesterone and increase in estrogen levels precedes the onset of labour.[14] These findings of changes in progesterone/estrogen (P/E) ratio are consistent with the concept of 'progesterone block', which was advanced and championed by Csapo[15] in the 1950s based on his extensive and pioneering experiments in pregnant rabbits.

The role of progesterone or of changes in P/E ratio in humans and other nonhuman primates is less well known. Although investigators have described low progesterone levels or low P/E ratios in the plasma of women destined to deliver prematurely,[16,17] no consistent evidence exists of changes in plasma progesterone or P/E ratio prior to the onset of labour at term or prior to term. Nonetheless, some evidence exists that local changes in progesterone or P/E ratio in the placenta, decidua or fetal membranes may be important in the initiation of labour in humans.[18]

Two separate investigators have described lower P/E ratios in the amniotic fluid of women in spontaneous labour compared with controls not in labour.[19,20] Recent reports by several groups have demonstrated that an increase in salivary estrogen

levels and/or change in salivary P/E ratios occurs prior to the onset of labour at term and prior to the onset of preterm labour.[21,22] These findings suggest that salivary measurement of steroids may be a more reliable indicator of biological effect and not subject to the wide minute-to-minute fluctuations known to occur in plasma levels of progesterone, estriol and estradiol in human pregnancy.[23]

Several investigators have reported the effects of administering progesterone antagonists to women at term. The results were an increased rate of spontaneous onset of labour and, in the women whose labour was induced with oxytocin, an increased sensitivity to oxytocin compared with placebo-treated controls.[24-26]

Although these data support the concept that progesterone plays a role in maintaining gestation in humans, the actual mechanisms by which progesterone therapy may avert preterm labour and delivery are not known.

3. Trials of Progestogens Given Prophylactically to Prevent Preterm Birth

The earliest trials of progesterone therapy to improve pregnancy outcome focused on the prevention of spontaneous abortion in women thought to be at risk for this problem. However, some of these early trials also reported longer term outcomes of the pregnancies studied.

The first reported trial of progesterone to improve pregnancy outcome and which reported rates of preterm delivery was by Swyer and Daley[27] in 1953 (table I). This trial enrolled women with a history of two spontaneous abortions and randomly or alternately assigned them to receive either six progesterone pellets of 25mg each inserted into the gluteal muscles or no hormonal treatment. Although the main outcome of interest was spontaneous abortion, the investigators also reported rates of preterm delivery. Of the 60 progesterone-treated patients, 13 spontaneously aborted and two delivered preterm. The rates of occurrence of these outcomes were similar in the 53 control patients, with 12 spontaneous abortions and one preterm delivery.

In 1964, Goldzieher[28] enrolled 54 women who had had two consecutive miscarriages (with low or normal levels of pregnandiol excretion) and randomly assigned them to receive medroxyprogesterone 10mg or a placebo tablet daily (table I). Of the 31 placebo recipients, 26 delivered at term compared with 18 of 23 receiving medroxyprogesterone, a difference that was not statistically significant. The investigator did not report preterm birth but mentioned two cases of preterm labour in the medroxyprogesterone group and one case in the placebo group.

The first trial reporting the use of 17α-hydroxyprogesterone caproate to improve pregnancy outcome was that of LeVine[30] in 1964 (table I). This trial enrolled women with a history of three or more spontaneous abortions immediately prior to the index pregnancy. The main outcome of interest was spontaneous abortion but preterm delivery was also reported. The patients were alternately assigned to receive a weekly injection of 17α-hydroxyprogesterone caproate 500mg or a placebo injection starting before 16 weeks' gestation. The study was flawed by the method of allocation of participants and by the lack of intent-to-treat analysis. The outcomes were reported for only the 30 patients who continued the injections (56 started the trial). Of 15 patients treated with 17α-hydroxyprogesterone caproate, four aborted spontaneously and three delivered preterm (20%). Of the 15 placebo-treated patients, seven aborted spontaneously and three delivered preterm (20%).

In contrast to the studies of progesterone for preventing spontaneous abortion, investigators became interested in the potential of progesterone therapy to prevent preterm labour and delivery. The first of these was Papiernik[31] in 1970.

Papiernik[31] employed a high-risk pregnancy scoring system to identify 99 women whose pregnancies were at risk for preterm birth. These 99 women were randomly assigned to treatment with 17α-hydroxyprogesterone caproate 250mg or placebo injections. The treatment was begun at 28–32 weeks' gestation and the schedule was for injections every three days for a total of eight doses. Preterm

Table I. Characteristics of trials reporting data on prevention of preterm delivery using progestogens

Study (year)	Inclusion criteria	Randomisation/ blinding	Use of placebo	Drug and dosage	Initiation/ending	Number of participants (treatment/ control)	Exclusion from analysis	Comments
Medroxyprogesterone								
Goldzieher[28] (1964)	History of two consecutive miscarriages	Yes/yes	Yes	PO MED 10mg tablets daily	<18 weeks' gestation/delivery or abortion	23/31	0	The end of treatment is not stated
Hobel et al.[29] (1994)	High-risk pregnancies (scoring system)	Yes/yes	Yes	PO MED 20mg tablets daily	20–31/37 weeks' gestation	411/412	0	Blocked randomisation scheme
Progesterone								
Swyer and Daley[27] (1953)	History of ≥2 abortions	In some cases; in others, alternately assigned/no	No	PRO 25mg pellets within the gluteal muscle (implants)	Before the tenth week of pregnancy/ delivery or abortion	60/53	0	
da Fonseca et al.[1] (2003)	Previous preterm birth, prophylactic cerclage or uterine malformation	Yes/yes	Yes	Natural PRO 100mg intravaginal suppositories daily	24/34 weeks	Initially included 157. Final results were measured in 72 treated and 70 controls	15	Exclusions were due to PPROM, allergy or therapeutic preterm delivery
17α-hydroxyprogesterone								
LeVine[30] (1964)	History of three consecutive miscarriages previous to current pregnancy	No (alternately)/ yes	Yes	IM 17P 500mg weekly injections	≤16/36 weeks	Initially included 56. Final results were measured in 15 treated and 15 controls	26	16 patients were not pregnant and 10 left the study before end
Papiernik[31] (1970)	High risk for preterm birth	Yes/yes	Yes	IM 17P 250mg injections every 3 days	28–32 weeks/ after 8 doses	99/99	0	

Continued next page

Table I. Contd

Study (year)	Inclusion criteria	Randomisation/ blinding	Use of placebo	Drug and dosage	Initiation/ending	Number of participants (treatment/ control)	Exclusion from analysis	Comments
Johnson et al.[32] (1975)	≥2 preterm births, abortion or a combination	Yes/yes	Yes	IM 17P 250mg once weekly	As soon as they registered/37 weeks	Initially included 43. Results measured in 18 treated and 22 controls	3	
Yemini et al.[33] (1985)	Current pregnancy immediately preceded by ≥2 preterm births, abortion or a combination	Yes/yes	Yes	IM 17P 250mg once weekly	As soon as they registered/37 weeks	Initially included 80. Final results were measured in 39 treated and 40 controls	1	All patients (treated and controls) also received a cervical cerclage
Suvonnakote[34] (1986)	≥2 midtrimester abortions, one preterm birth, or a combination	No/no	No	IM 17P 250mg once weekly	16–20/37 weeks	36/39	0	Controls were not random women with similar characteristics
Hartikainen-Sorri et al.[35] (1980)	Women with twin pregnancies without signs of premature labour	NS/yes	Yes	IM 17P 250mg once weekly	28–33/37 weeks	39/38	0	The investigator did not mention method of randomisation
Hauth et al.[36] (1983)	Low-risk pregnancies	Yes/yes	Yes	IM 17P 1000mg once weekly	16–20/36 weeks	80/88	0	Patients who declined to participate were also followed up
Meis et al.[2] (2003)	Documented previous spontaneous preterm delivery	Yes/yes	Yes	IM 17P 250mg once weekly	16–20/37 weeks	310/153	0	The study was halted at 463 participants due to the evidence of efficacy

17P = 17α-hydroxyprogesterone caproate; **IM** = intramuscular; **MED** = medroxyprogesterone; **NS** = not stated; **PO** = oral; **PPROM** = preterm premature rupture of fetal membranes; **PRO** = progesterone.

delivery was significantly less frequent in the treatment group (4%) compared with placebo group (18%). Papiernik wished to pursue a larger, more definitive trial of 17α-hydroxyprogesterone caproate but was unable to secure funding for this study (Papiernik E, personal communication).

In 1975, Johnson et al.[32] reported the results of a trial of 17α-hydroxyprogesterone caproate for women who had a history of two spontaneous abortions, two preterm deliveries or a combination of these outcomes in the pregnancies immediately preceding the index pregnancy. Of the 43 women, 18 were randomised to weekly injections of 17α-hydroxyprogesterone caproate 250mg and 22 were randomised to placebo injections. The treatment was started as soon as the patients registered for care, and were continued to 37 weeks' gestation. Three patients in the placebo group and four patients in the treatment group also received a cervical cerclage. The primary outcome was delivery at <36 weeks' gestation. The rate of preterm delivery in the placebo group was 41% (nine women), whereas none of the treatment group delivered before 36 weeks. The treatment group showed significant differences with the control group in mean duration of pregnancy ($p < 0.025$), mean birthweight ($p < 0.025$) and perinatal mortality rate ($p < 0.05$). The trial can be criticised for the rather broad inclusion criteria and by the use of cerclage for a minority of the subjects. The investigators concluded that large-scale trials were needed to demonstrate the efficacy of this treatment. However, the publication of this trial in a major medical journal stimulated considerable interest in the use of this drug to prevent preterm birth. No support for a larger, more definitive trial was available and the funding agency felt that, in view of the positive results of the trial, a further placebo-controlled trial could not be ethically supported.[17]

In 1985, Yemini et al.[33] reported the results of a trial of 17α-hydroxyprogesterone caproate and cervical cerclage for treating women at risk for preterm delivery. Eighty women were enrolled who had a history of two spontaneous abortions, two preterm births or a combination of these outcomes in their preceding pregnancies. All patients received an ultrasound examination to verify a live fetus and to confirm gestational age. The patients were randomly assigned to weekly injections of 17α-hydroxyprogesterone caproate 250mg or a placebo inert oil until 37 weeks' gestation. All patients received a cervical cerclage. Of the 79 patients who completed the study, the rate of the preterm delivery in the treatment group was significantly lower (16.1%) compared with the placebo group (37.8%; $p < 0.05$). The mean birthweight in the treatment group was higher than in the placebo group. This trial differs from others in that all the subjects received a cervical cerclage. It is uncertain whether the results were influenced by the use of cerclage.

Suvonnakote[34] reported the results of a trial of 17α-hydroxyprogesterone caproate in 1986. Thirty-six patients with a history of one previous preterm delivery, two midtrimester spontaneous abortions or a combination of these were treated from 16–20 weeks' gestation up to 37 weeks with weekly injections of 17α-hydroxyprogesterone caproate. The results were compared with a group of 39 controls with similar characteristics. The selection was not random and no placebo was used. The rate of preterm delivery was significantly lower, 14%, in the treatment group compared with 49% in the control group ($p = 0.0036$). The lack of randomisation and of a placebo control group diminishes the value of this report.

Although the aforementioned trials employing 17α-hydroxyprogesterone caproate showed positive results for the prevention of preterm birth, two trials did not show positive results. In 1980, Hartikainen-Sorri et al.[35] reported the results of a trial in twin pregnancies where 77 women who were identified to have twin gestations at between 28–33 weeks and were then randomly assigned to receive weekly injections of either 17α-hydroxyprogesterone caproate 250mg or a placebo until 37 weeks' gestation. No significant differences were seen for rates of preterm delivery (30.8% in the treatment group versus 23.7% in the placebo group), mean duration of pregnancy, mean birthweight or rates of perinatal mortality. To date, this remains the only reported trial of 17α-hydroxyprogesterone caproate or other

progestogen in multiple gestation. The lack of efficacy may have been related to the relatively late gestational age at which treatment was initiated.

Hauth et al.[36] reported the results of a trial of 17α-hydroxyprogesterone caproate in a relatively low risk group of pregnant women in 1983. The selection of subjects for this trial was of women on active duty in the military. The women were randomly assigned at 16–20 weeks' gestation to receive weekly injections of 17α-hydroxyprogesterone caproate 1000mg (n = 80), or a placebo (88), until 36 weeks' gestation. No difference was seen for any pregnancy outcome studied. The rate of low birthweight birth for the treatment group was 7.5% compared with 9% for babies in the placebo group. The results of this trial are notable for the low rate of preterm or low birthweight delivery in the population studied. Because of the low prevalence of the outcome variable in this population, the trial did not have sufficient power to detect a difference in rates of low birthweight birth. To show a 40% reduction in the treatment group compared with placebo in the rate of the outcome measured (low birthweight) would have required a total sample of 1540 subjects. The results of this trial suggest that progesterone therapy is not useful in women at low risk for preterm delivery.

The results of these early reported trials were evaluated by two different meta-analyses. Goldstein et al.[37] published the results of a meta-analysis of randomised controlled trials involving the use of progesterone or other progestogenic agents for the maintenance of pregnancy in 1989. Fifteen trials of variously defined high-risk subjects were felt to be suitable for analysis. The trials employed six different progestational drugs. The pooled odds ratios for these trials showed no statistically significant effect on rates of miscarriage, stillbirth, neonatal death or preterm birth. The authors concluded that 'progestogens should not be used outside of randomised trials at present'.

In response to this publication, the following year Keirse[38] presented the results of an analysis of a more focused selection of trials. This meta-analysis was restricted to trials that employed 17α-hydroxyprogesterone caproate, the most fully studied progestational agent, and included all placebo-controlled trials which used this drug. Pooled odds ratios showed no significant effect on rates of miscarriage, perinatal death or neonatal complications. However, in contrast to Goldstein's review, the odds ratio for preterm birth was significant, 0.5 (95% CI 0.30, 0.85), as was the odds ratio for birthweight <2500g, 0.46 (95% CI 0.27, 0.80). Keirse[38] remarked that the results demonstrated by these trials contrast markedly with the poor effectiveness of other efforts to reduce the occurrence of preterm birth, but that since no effect was demonstrated to result in lower perinatal mortality or morbidity, "further well-controlled research would be necessary before it is recommended for clinical practice".

A large trial of an oral progestogen was reported by Hobel et al.[29] in 1994. As part of a larger preterm birth prevention programme, 823 patients were identified as being at risk for preterm birth by a high-risk pregnancy scoring system. The drug used was medroxyprogesterone (Provera® [1], Pharmacia & Upjohn, New York, NY, USA) and 411 patients were assigned to take 20mg tablets orally daily. The control group of 412 patients were given placebo tablets. The allocation to drug or placebo was on the basis of the particular prenatal clinic the patient attended. The women were enrolled prior to 31 weeks' gestation. The outcome of interest was delivery at <37 weeks. The rate of preterm delivery in the treatment group was 11.2% compared with 7.3% in the placebo group. The rate of compliance for the subjects was low, with only 55% of the patients assigned to the medroxyprogesterone group actually taking the drug.

Recently, two large trials have been reported of the use of progestogens to prevent preterm birth.

The results of a randomised, placebo-controlled trial of vaginal progesterone suppositories in 142 women was reported by da Fonseca et al.[1] The participants were identified as being at high risk for preterm birth. The risk factor in over 90% of the subjects was that of a previous preterm delivery. The

1 The use of trade names is for product identification purposes only and does not imply endorsement.

patients were randomly assigned to daily insertion of either a progesterone 100mg suppository or a placebo suppository. The treatment period was until 24–34 weeks' gestation. All patients were monitored for uterine contractions once a week for 1 hour with an external tocodynamometer. Although 81 progesterone- and 76 placebo-treated patients were included into the study, several patients were excluded from analysis because of premature rupture of the fetal membranes, or were lost to follow-up, leaving 72 and 70 in the progesterone and placebo groups, respectively. The rate of preterm delivery <37 weeks in the progesterone-treated patients was 13.8%, significantly less than the rate in the placebo-treated patients of 28.5%. The rate of preterm delivery <34 weeks in the treatment group was 2.8% compared with 18.6% in the placebo group. These differences were statistically significant (all $p < 0.05$). The rate of uterine contractions measured by the weekly hour-long recording was significantly less between 28 and 34 weeks in the progesterone recipients compared with the placebo ($p < 0.004$). Analysis of the results by intent to treat showed smaller differences between the groups but these differences remained statistically significant.

Meis et al.[2] reported the results of a large multicentre trial of 17α-hydroxyprogesterone caproate conducted by the Maternal Fetal Medicine Units Network of the National Institute of Child Health and Human Development, Bethesda, MD, USA. The study enrolled women with a documented history of a spontaneous preterm delivery that occurred as a consequence of either spontaneous preterm labour or preterm premature rupture of the fetal membranes. After receiving an ultrasound examination to rule out major fetal anomalies and determine gestational age, the women were offered the study and given a test dose of the placebo injection to assess compliance. If they chose to continue they were randomly assigned, using a 2 : 1 ratio, to weekly injections of 17α-hydroxyprogesterone caproate 250mg or placebo. Treatment was begun between 16 and 20 weeks' gestation and was continued until delivery or 37 weeks' gestation, which ever came first. The study planned to enrol 500 participants, a sample size estimated to be sufficient to detect a 37% reduction in the rate of preterm birth. However, enrolment was halted at 463 patients – 310 in the treatment group and 153 in the placebo group – following a scheduled evaluation by the Data Safety and Monitoring Committee, which found that the evidence of efficacy for the primary outcome was such that further entry of patients was unnecessary. In this study, delivery at <37 weeks was reduced from 54.9% in the placebo group to 36.3% in the treatment group ($p < 0.001$). Similar reductions were seen in delivery at <35 weeks, from 30.7% to 20.6% ($p = 0.02$), and in delivery at <32 weeks, from 19.6% to 11.4% ($p = 0.02$). All these differences were statistically significant. Rates of birthweight <2500g were significantly reduced ($p = 0.003$), as were rates of intraventricular haemorrhage, necrotising enterocolitis, and need for supplemental oxygen and ventilatory support. Rates of neonatal death were reduced from 5.9% in the placebo group to 2.6% in the treatment group, although this difference did not reach statistical significance. The women enrolled in this study had unusually high rates of preterm birth. This could be explained in part by the fact that the mean gestational age of their previous preterm delivery was quite early, at 31 weeks. In addition, one-third of the women had had more than one previous spontaneous preterm delivery. Despite random allocation, more women in the placebo group had had more than one preterm delivery. Adjustment of the analysis controlling for the imbalance found that the treatment effect remained significantly different than with placebo (relative risk 0.70; 95% CI 0.57, 0.85). A majority of the women were of African American ethnicity and the treatment with 17α-hydroxyprogesterone caproate showed equal efficacy in the African American women and in the non-African American subjects.

4. Trials of Progesterone as a Tocolytic Drug

Trials studying the use of progesterone as a tocolytic drug are summarised in table II. Fuchs and Stademann[39] in 1960 assigned by admission num-

Table II. Characteristics of trials reporting data on the use of progestogens as tocolytic drugs

Study (year)	Inclusion criteria	Randomisation/ blinding	Use of placebo	Drug and dosage	Initiation/ending	Number of participants (treatment/ control)	Exclusion from analysis	Comments
Fuchs and Stademann[39] (1960)	Threatened preterm labour	No (assigned by admission)/yes	Yes	IM crystalline PRO 200mg daily for 3 days, 150mg daily for 2 days and 100mg daily thereafter	After a period of observation of 2–24 hours after admission/ 1 week after symptoms disappeared	63/63	3	
Kaupilla et al.[40] (1980)	Threatened preterm labour	No/no	No	IM 17P 250mg once weekly, hydrocortisone	27–36/37 weeks	24/24	0	
Erny et al.[41] (1986)	Threatened preterm labour	Yes/yes	Yes	PO micronised PRO 400mg	30–36 weeks/until discharge (if contractions decreased, if not β_2-adrenoceptor agonists were used)	29/28	0	The study did not report preterm delivery
Noblot et al.[42] (1991)	Threatened preterm labour	Yes/yes	Yes	PO micronised PRO (400mg every 6 hours the first day, 400mg every 8 hours the second day, and 300mg every 8 hours the third day)	<35 weeks/3 days after	22/22	0	All patients also received treatment with ritodrine
Brenner and Hendricks[43] (1962)	Pregnant women 36–38 weeks	Yes/yes	Yes	Oral MED 20mg four times daily	36–38 weeks/delivery	98/97	5	The study evaluated length of pregnancy

17P = 17α-hydroxyprogesterone caproate; **IM** = intramuscular; **MED** = medroxyprogesterone; **PO** = oral; **PRO** = progesterone.

ber 126 patients with symptoms of threatened premature labour to receive in blinded fashion either progesterone in oil 50mg four times daily for 3 days, or placebo injections. On the fourth and fifth days the women received the progesterone or placebo three times daily, and then subsequently twice daily. No difference was found in prolongation of pregnancy between the progesterone and placebo groups. Rates of low birthweight were also not different.

In 1980, Kaupilla et al.[40] treated two consecutive groups of 24 women each in threatened premature labour with progesterone and ritodrine. The first group received intramuscular 17α-hydroxyprogesterone caproate 250mg and intravenous hydrocortisone 100mg. The hydrocortisone treatment was repeated on the second and third day and 17α-hydroxyprogesterone caproate was given on day 3 and subsequently at weekly intervals. The second group were treated with intravenous ritodrine for 48 hours followed by intramuscular ritodrine 20mg three times daily for 2 days. Prolongation of pregnancy >7 days occurred in 87.5% of the progesterone and hydrocortisone group and in 75% of the ritodrine group. These differences were not statistically significant. Most of the women delivered at term. In the absence of a placebo group, the possibility cannot be excluded that many of these women were not actually in labour and that the prolongation of pregnancy was not an effect of drug treatment.

In 1986, Erny et al.[41] treated 57 patients at 30–36 weeks' gestation who were at risk of preterm labour. The patients were monitored for 1 hour and then randomly assigned to receive oral micronised progesterone 400mg or a placebo. After 1 hour the protocol was ended and the patients received intravenous ritodrine for tocolysis. The frequency of contractions decreased in 76% of the progesterone group and in 43% of the placebo group. No data on prolongation of pregnancy was reported.

In 1991 Noblot et al.[42] treated 44 patients at <35 weeks' gestation who were in apparent premature labour. All were treated with ritodrine and, additionally, randomly assigned to receive either micronised progesterone 400mg or a placebo every 6 hours for the first day, then every 8 hours for the second day, then either progesterone 300mg or placebo every 8 hours subsequently. No difference was found between the two groups for prolongation of pregnancy or in the rate of preterm birth. Only 14 of the 44 women delivered preterm, raising the suspicion that many may not have been in true labour.

Brenner and Hendricks[43] reported a trial in 1962 that examined whether progesterone could prolong pregnancy if given to women near term. The investigators enrolled 200 women who were between 36 and 38 weeks' gestation, and randomly assigned them to receive medroxyprogesterone 20mg or placebo tablets four times daily. No difference was found in the gestational age at delivery or the mean length of labour.

The results of these trials suggest that progesterone therapy has no significant effectiveness when used to halt labour or as adjuncts to the use of other drugs to stop labour.

5. Conclusion

Among the several progestational compounds employed in trials of prematurity prevention, 17α-hydroxyprogesterone caproate has shown the greatest promise, with six trials showing success in women with singleton pregnancies who were at high risk for preterm delivery. The only reported negative trials of this compound were in women with twin pregnancies or women at low risk for preterm delivery. An alternative treatment using progesterone suppositories was reported to be successful in one trial. Little information is available about the efficacy of other progestational compounds in preventing preterm delivery. None of the published trials have reported significant adverse effects, other than local irritation or pain at the site of injections.

All the published successful trials have initiated therapy relatively early in gestation (at <24 weeks) in women who showed no symptoms of preterm labour. Trials of progesterone compounds to aid in halting the progression of labour have not been successful, and the use of progesterone in women who have had symptoms or signs of labour should be discouraged. The trials that have been successful

have enrolled women with singleton pregnancies and who were at high risk for preterm delivery because of their past pregnancy outcomes (one or more prior preterm deliveries or recurrent miscarriage). The efficacy of preventing preterm delivery in multiple gestations remains unproven, with the only published trial reporting negative results. The use of progesterone treatment for women with other risk factors is unproven and should be discouraged outside of randomised trials.

Thus, progesterone treatment has shown efficacy in preventing recurrent preterm delivery in women with singleton gestations. This group of women, constituting approximately 10% of the total of pregnant women, accounts for only a fraction of all preterm births. While progesterone treatment to prevent preterm delivery cannot at present be considered standard of care, many clinicians may decide that sufficient evidence of efficacy exists to use this drug for this specific group of women. It is hoped that future trials may broaden the indications for this treatment, which remains the only proven effective prevention method for this important problem.

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References

1. da Fonseca EB, Bittar RE, Carvalho MHB, et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol 2003; 188: 419-24
2. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003; 348: 2379-85
3. Paneth NS. The problem of low birth weight. Future Child 1995; 5: 19-34
4. Mattison DR, Damus K, Fiore E, et al. Preterm delivery: a public health perspective. Paediatr Perinat Epidemiol 2001; 15 Suppl. 2: 7-16
5. Gyetvai D, Hannah ME, Hodnett ED, et al. Tocolytics for preterm labor: a systematic review. Obstet Gynecol 1999; 94: 869-77
6. Harger JH. Cerclage and cervical insufficiency: and evidence-based analysis. Obstet Gynecol 2002; 100: 1313-27
7. Carey JC, Klebanoff MA, Hauth JC, et al. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic vacterial vaginosis. N Engl J Med 2000; 342: 534-40
8. Klebanoff MA, Carey JC, Hauth JC, et al. Failure of metronidazole to prevent preterm delivery among pregnant women with asyptomatic *Trichomonas Vaginalis* infection. N Engl J Med 2001; 345: 487-93
9. Creasy RK. Preterm birth prevention: where are we? Am J Obstet Gynecol 1993; 168: 1223-30
10. Rebar RW, Cedars MI. Hypergonadotropic forms of amenorrhea in young women. Endocrinol Metab Clin North Am 1992 Mar; 21 (1): 173-91
11. Stites SP, Siiteri PK. Steroids as immunosppressants in pregnancy. Immunol Rev 1983; 75: 117-38
12. Siiteri PK, Seron-Ferre M. Some new thoughts on the feto-placental unit and parturition in primates. In: Novy JM, Reskko AJ, editors. Fetal endocrinology. New York: Academic Press, 1981: 1-34
13. Garfield RE, Dannan MS, Daniel EE. Gap junction formation in myometrium: control by estrogens, progesterone, and prostaglandins. Am J Physiol 1980; 238: C81-9
14. Challis JR. Sharp increase in free circulating oestrogens immediately before parturition in sheep. Nature 1971; 229: 208
15. Csapo AI. Progesterone 'block'. Am J Anat 1956; 98: 273-91
16. Cousins LM, Hobel CJ, Chang RJ, et al. Serum progesterone and estradiol-17β levels in premature and term labor. Am J Obstet Gynecol 1977; 127: 612-5
17. Johnson JWC, Lee PA, Zachary AS, et al. High-risk prematurity-progestin treatment and steroid studies. Obstet Gynecol 1979; 54: 412-8
18. Mitchell B, Cruickshank B, McLain D, et al. Local modulation of progesterone production in human fetal membranes. J Clin Endocrinol Metab 1982; 55: 1237-9
19. Romero R, Scoccia B, Mazor M, et al. Evidence for a local change in the progesterone/estrogen ratio in human parurition at term. Am J Obstet Gynecol 1988; 159: 657-60
20. Mazor M, Wiznitzer A, Levy J, et al. The relationship between estrogen/progesterone ratio and term human parturition. Isr J Med Sci 1993; 29: 97-9
21. Darne J, McGarrigle HHG, Lachelin GCL. Saliva oestriol, oestradiol, oestrone and progesterone levels in pregnancy: spontaneous labor at term is preceded by a prise in the saliva oestriol: progesterone ratio. Br J Obstet Gynaecol 1987; 94: 227-35
22. Jackson GM, McGregor JA, Lachelin GCL, et al. Salivary estriol rise predicts preterm labor. Am J Obstet Gynecol 1995; 172: 406
23. Buster JE, Meis PJ, Hobel CJ, et al. Subhourly variability of circulating third trimester maternal steroid concentrations as a source of sampling error. J Clin Endocrinol Metab 1978; 46: 907-10
24. Frydman R, LeLaidier C, Baton C, et al. Labor induction in women at term with mifepristone (RU 486): a double-blind, randomized, placebo-controlled study. Obstet Gynecol 1992; 80: 972-5
25. LeLaidier C, Baton C, Beniifla JL, et al. Mefipristone for labour induction after previous caesarean section. Br J Obstet Gynecol 1994; 101: 501-3
26. Chwalisz K, Fahrenholz F, Hackenbery M, et al. The progesterone antagonist onapristone increases the effectiveness of oxytocin to produce delivery without changing the myometrial oxutocin receptor concentrations. Am J Obstet Gynecol 1991; 165: 1760-70
27. Swyer GIM, Daley D. Progesterone implantation in habitual abortion. BMJ 1953 May 16; 1 (4819): 1073-7

28. Goldzieher J. Double-blind trial of a progestin in habitual abortion. JAMA 1964; 188: 651-4
29. Hobel CJ, Ross MG, Bemis RL, et al. The West Los Angeles Preterm Birth Prevention Project. I: program impact on high-risk women. Am J Obstet Gynecol 1994; 170: 54-62
30. LeVine L. Habitual abortion: a controlled clinical study of pregestational therapy. World J Surg 1964; 72: 3036
31. Papiernik E. Double blind study of an agent to prevent pre-term delivery among women at increased risk [in French]. Edition Schering 1970; Serie IV, fiche 3: 65-8
32. Johnson JWC, Austin KL, Jones GS, et al. Efficacy of 17 alpha-hydroxyprogesterone caproate in the prevention of premature labor. N Engl J Med 1975; 292: 675-80
33. Yemini M, Borenstein R, Dreazen E, et al. Prevention of premature labor by 17 alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol 1985; 151: 574-7
34. Suvonnakote T. Prevention of pre-term labour with progesterone. J Med Assoc Thailand 1986; 69: 538-42
35. Hartikainen-Sorri AL, Kauppila A, Tuimala R. Inefficacy of 17 alpha hydroxyprogesterone caproate in the prevention of prematurity in twin pregnancy. Obstet Gynecol 1980; 56: 692-5
36. Hauth JC, Gilstrap LC, Brekken AL, et al. The effect of 17 alpha-hydroxyprogesterone caproate on pregnancy outcome in an active-duty military population. Am J Obstet Gynecol 1983; 146: 187-19
37. Goldstein P, Berrier J, Rosen S, et al. A meta-analysis of randomized control trials of progestational agents in pregnancy. Br J Obstet Gynecol 1989; 96: 265-74
38. Keirse MJNC. Progesterone administration in pregnancy may prevent pre-term delivery. Br J Obstet Gynecol 1990; 97: 149-54
39. Fuchs F, Stademann G. Treatment of threatened premature labor with large doses of progesterone. Am J Obstet Gynecol 1960; 79: 172-6
40. Kaupilla A, Hartikainen-Sorri A-L, Olli J, et al. Suppression of threatened premature labor by administration of cortisol and 17 alpha-hydroxyprogesterone caporate: a comparison with ritodrine. Am J Obstet Gynecol 1980; 138: 404-8
41. Erny R, Pigne C, Prouvost M, et al. The effects of oral administration of progesterone for premature labor. Am J Obstet Gynecol 1986; 154: 525-9
42. Noblot G, Audra P, Dargent D, et al. The use of micronized progesterone in the treatment of menace of preterm delivery. Eur J Obstet Gynecol Reprod Biol 1991; 40: 203-9
43. Brenner WE, Hendricks CH. Effect of medroxyprogesterone acetate upon the duration and characteristics of human gestation and labor. Am J Obstet Gynecol 1962; 83: 1094-8

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