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The changing role of progesterone in preterm labour

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Progesterone is an essential hormone in the process of reproduction. It is involved in the menstrual cycle, implantation and is essential for pregnancy maintenance. Although the pharmacokinetics and pharmacodynamics of progesterone have been well studied, and since 1935 it has been synthesised and is now available commercially, its use in the pathophysiology of pregnancy remains controversial. One of these concerns is the way in which the hormone is administered, with parenteral use proving the best way to obtain optimal plasma levels. Another concern is the paucity of randomised controlled trials and the different dosages and populations studied. As a result, the therapeutic application of progesterone in pregnancy is restricted to the prevention and treatment of threatened miscarriage, recurrent miscarriage and preterm birth. Progesterone is efficacious when continuation of pregnancy is hampered by immunological factors, luteinic and neuroendocrine deficiencies and myometrial hypercontractility. This may explain the reduction in the incidence of preterm birth in high risk pregnant women using high-dosage prophylactic progesterone.

INTRODUCTION

Since the synthesis of progesterone in 1935, no other drug has been so extensively studied. Progesterone has been proposed and used in the treatment of different gynaecological pathologies, such as endometrial hyperplasia, dysfunctional uterine bleeding, amenorrhoea, luteal phase deficiency and premenstrual syndrome, as well as being used as a contraceptive tool alone or in combination with oestrogens, for assisted reproductive technologies and in pregnancy maintenance.[1]

Progesterone can be administered by three routes: orally, vaginally or intramuscularly. Oral administration guarantees optimal compliance by patients but shows many disadvantages. Firstly, there is extreme variability in the plasma concentrations obtained due to individual variability in gastric filling and enterohepatic circulation. The oral route also results in side effects such as nausea, headache, sleepiness, etc. The vaginal route results in higher concentrations in the uterus but does not reach high and constant blood levels. Progesterone administered intramuscularly occasionally induces non-septic abscesses, but it is the only route which results in optimal blood levels.[1]

The mechanism of action of progesterone is through specific cytoplasmatic receptors, which are influenced by the concentrations of oestradiol (Figs 1–3). This paper will discuss the pros and cons of progesterone use in pregnancy, particularly with respect to the management of women with threatened miscarriage, recurrent miscarriage and preterm labour.

THREATENED MISCARRIAGE

The various aetiologies of spontaneous abortion make it difficult to prevent and manage the condition. A high percentage of the so-called 'threatened miscarriages' settle spontaneously as a result of bed rest and/or no treatment, and vaginal bleeding in early pregnancy is not synonymous with threatened miscarriage. By varying the inclusion or exclusion criteria for any given protocol, the results of a study treatment can be altered completely. This should not discourage treatment but should encourage an appropriate diagnosis and treatment aimed to counteract the underlying pathology.

One possible way is to decrease or to stop uterine contraction. Progesterone has been shown to possess a tocolytic action on the myometrium both *in vitro* and *in vivo*

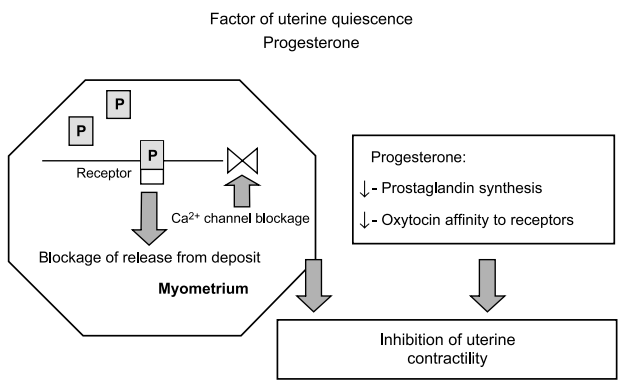

Fig. 1. Progesterone and uterine contractility: mechanisms of action.

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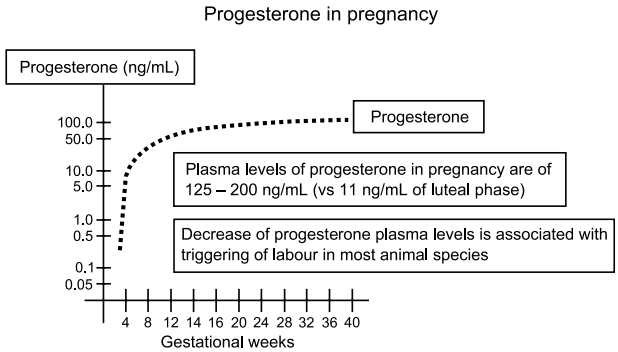

Fig. 2. Progesterone levels and uterine contractility in pregnancy.

during the pregnancy.[1–3] Progesterone has also been shown *in vivo* to be concentration dependent.[3] Daily administration of 100 mg of progesterone intramuscularly results in 0.6 γ/g of endometrial and myometrial tissue.

Only high-dosage progesterone exerts a tocolytic action in early pregnancy and, according to patient weight, the optimal dose should be between 100 and 200 mg/day.[4] This dosage has also proven effective in the maintenance of uterine quiescence during cervical cerclage (during the first trimester of pregnancy) and/or following abdominal surgery (e.g. appendectomy).

RECURRENT MISCARRIAGE

Recurrent miscarriage is defined as three consecutive pregnancy losses. Extensive investigation of the women involved will fail to find a recognisable cause in up to half of cases.[5] Luteal phase defects and immunotolerance derangements are the most common recognisable causes.[6,7] Progesterone possesses favourable immunotolerant actions

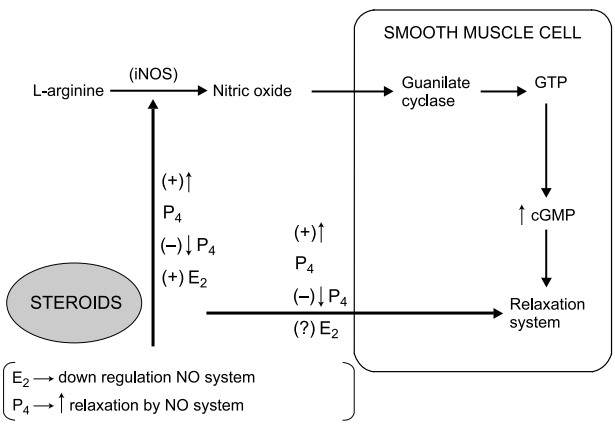

Fig. 3. Hormonal regulation of smooth muscle cell function. Interaction between progesterone and nitric oxide.

Table 1. Efficacy of progesterone in support of recurrent miscarriages: meta-analysis of RCTs.[12]

Randomised Controlled Trials	Odds ratio (95% CI)
Tognoni *et al.*[9]	1.29 (0.87–1.51)
Gerhard *et al.*[10]	0.56 (0.13–2.49)
Reijinders[11]	1.99 (0.20–19.66)
Total	1.28 (0.50–6.49)

by stimulating the production of progesterone-induced blocking factor against natural killer cells whose activity is crucial to implantation and the interaction between the conceptus and the host in early pregnancy.[8] A protocol based on the administration of progesterone (intramuscularly or vaginally, from 100 to 400 mg/day) was developed and has been evaluated in a few randomised controlled trials.[9–11] The results showed a slight but significant efficacy compared with placebo (Table 1).[12] Similar results were obtained in proven luteal phase defects, where progesterone treatment should be started as early as possible after ovulation or, in assisted reproduction techniques, after insemination or embryo transfer.[13–16]

PRETERM LABOUR

Csapo proposed the see-saw theory (Fig. 4) 40 years ago, which stated that progesterone is implicated in the mechanism of human parturition (at term and preterm) with different outcomes (Fig. 5).

Adequate progesterone concentrations in myometrium are able to counteract prostaglandin stimulatory activity as well as oxytocin properties that enhance the activity of β-agonists.[17] Progesterone decreases the concentration of myometrial oxytocin receptors, which counteract the effect of oestrogens. The same is true with respect to the number and properties of gap junctions. Progesterone also inhibits

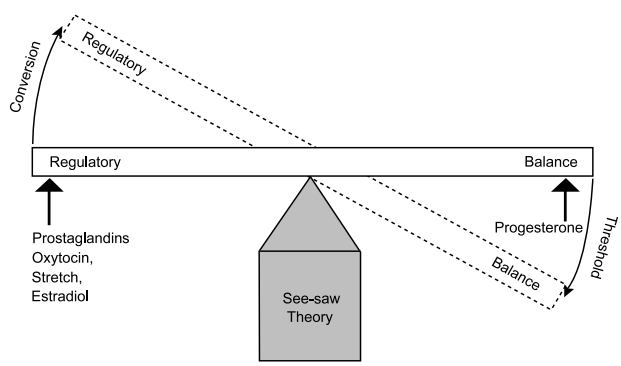

Fig. 4. Csapo's 'see-saw theory'. Progesterone withdrawal is the signal for parturition.

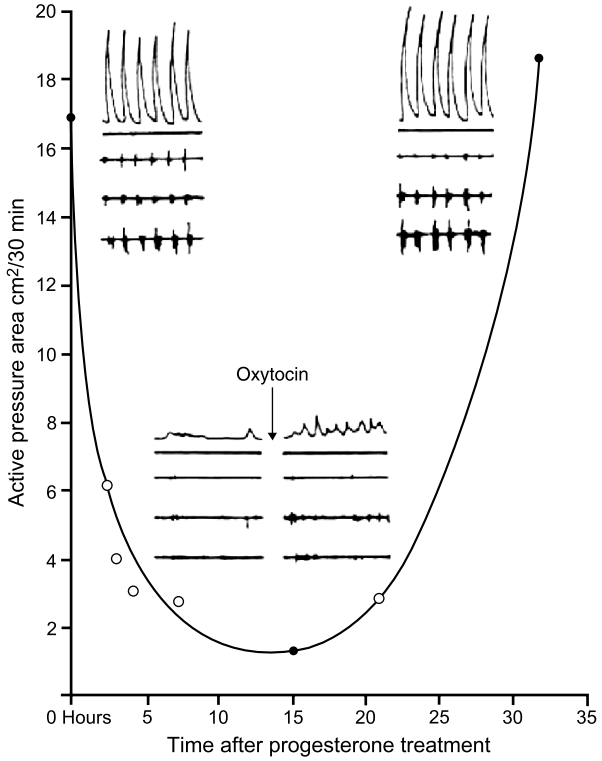

Fig. 5. Suppression of electrical activity of the uterus and the intrauterine pressure by progesterone therapy (5 mg in oil, intramuscularly) and the recovery of activity after progesterone withdrawal. The active pressure area is the area under the active pressure curve. Note the following: (i) the synchrony in electrical activity and the uncomplicated shape of the pressure curve before progesterone administration and after recovery (ii) that at the peak of progesterone effect (15 hours after progesterone treatment) the electrical activity, pressure and oxytocin response are all greatly suppressed, for all that is left is local rather than propagated activity.

prostaglandin production by amnion–chorion–decidua and has been shown to increase the binding of progesterone in the fetal membranes at term, which may explain the predominant effect of oestrogen in promoting prostaglandin production and triggering labour.

Table 2. Clinical results of the association of β-agonists and progesterone for the treatment of preterm labour (Di Renzo *et al.*, unpublished data, 2003).

	β-agonists	β-agonists + progesterone
Number of women	47	42
Gestational age (weeks [SD])	30.5 [3.2]	30.3 [2.7]
Ritodrine dose	100 mg in saline (0.1–0.3 mg/min)	50 mg in saline (0.1–0.3 mg/min) + progesterone 200 mg/day
Delivery after 48 h	87%	85%
Delivery after 7 days	65%	68%

Table 3. Decrease of maternal side effects using β-agonists in combination with progesterone (Di Renzo *et al.*, unpublished data, 2003).

Maternal side effect	β-agonists (%)	β-agonists + progesterone (%)
Maternal tachycardia	97	52
Nausea and vomiting	28	16
Tremblings	26	12
Palpitations	32	22
Chest pain	15	10
Hyperglycaemia	77	28
Hypokalaemia	92	33

The administration of high-dosage progesterone has been advocated as a possible tocolytic agent but its action is slow and its use has been abandoned for acute tocolysis except in conjunction with β-agonists. The combination of the two drugs has shown synergistic effects by decreasing the need for high concentrations of β-agonists, which have potentially dangerous side effects (Tables 2 and 3).

The use of prophylactic progesterone at high doses has recently been proposed in women at high risk for preterm birth (one or more previous preterm births before 32 weeks) (Table 4). An NIH randomised controlled trial has shown that weekly administration of 17-α-hydroxyprogesterone caproate at 300 mg/day intramuscularly results in a decrease of almost 50% in the subsequent incidence of preterm birth before 32 and 36 weeks, irrespective of the aetiology.[18]

In conclusion, progesterone may be used either for acute tocolysis to decrease the concentration of potentially harmful tocolytic drugs, or as a preventive agent in a high risk population of women at risk of preterm birth.

CONCLUSION

We believe that there is a place for high-dose progesterone for the prevention of preterm birth. Progesterone is more effective if it is administered intramuscularly, in the three major pregnancy pathologies: threatened abortion, recurrent miscarriage and prevention of preterm birth. The beneficial effects can only be obtained with optimal dosage, route and timely delivery of the drug.

Table 4. Use of prophylactic progesterone in high risk patients for preterm labour.[18]

	Placebo	Progesterone	Relative risk	CI	*P* value
N	153	306			
<34 weeks	54%	36.3%	0.66	0.54–0.93	0.0001
<35 weeks	30.7%	20.6%	0.67	0.48–0.93	0.0165
<32 weeks	19.6%	11.4%	0.58	0.37–0.92	0.0180

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