Progesterone in normal and pathological pregnancy

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Abstract: Progesterone is an essential hormone in the process of reproduction. It is involved in the menstrual cycle, implantation and is essential for pregnancy maintenance. It has been proposed and extensively used in the treatment of different gynecological pathologies as well as in assisted reproductive technologies and in the maintenance of pregnancy. Called “the pregnancy hormone”, natural progesterone is essential before pregnancy and has a crucial role in its maintenance based on different mechanisms such as: modulation of maternal immune response and suppression of inflammatory response (the presence of progesterone and its interaction with progesterone receptors at the decidua level appears to play a major role in the maternal defense strategy), reduction of uterine contractility (adequate progesterone concentrations in myometrium are able to counteract prostaglandin stimulatory activity as well as oxytocin), improvement of utero-placental circulation and luteal phase support (it has been demonstrated that progesterone may promote the invasion of extravillous trophoblasts to the decidua by inhibiting apoptosis of extravillous trophoblasts). Once the therapeutic need of progesterone is established, the key factor is the decision of the best route to administer the hormone and the optimal dosage determination. Progesterone can be administered by many different routes, but the most utilized are oral, the vaginal and intramuscular administration. The main uses of progesterone are represented by: threatened miscarriage, recurrent miscarriage and preterm birth (in the prevention strategy, as a tocolytic agent and also in the maintenance of uterine quiescence).

Keywords: pathological pregnancy; pregnancy; preterm birth; progesterone; tocolysis.

Introduction

Progesterone is an essential hormone in the process of reproduction. It is involved in the menstrual cycle, implantation and is essential for pregnancy maintenance. It has been proposed and extensively used in the treatment of different gynecological pathologies, such as endometrial hyperplasia, dysfunctional uterine bleeding, amenorrhea, luteal phase deficiency and premenstrual syndrome, as well as in assisted reproductive technologies and in the maintenance of pregnancy, alone or in combination with estrogens or to prevent endometrial hyperplasia from unopposed estrogen in hormone replacement therapy [1]. A clear distinction should be made with so named progestins which are synthetic progestogens that have progestogenic effects similar to those of natural progesterone and are commonly used for hormonal contraception (either alone or with an estrogen).

Moreover, progesterone is also efficacious when continuation of pregnancy is hampered by immunological factors, lutein and neuroendocrine deficiencies and myometrial hypercontractility.

Role of progesterone

Called “the pregnancy hormone”, natural progesterone is essential before pregnancy and has a crucial role in its maintenance based on different mechanisms such as: modulation of maternal immune response [1–3] and suppression of inflammatory response [4], reduction of uterine contractility [5–7], improvement of utero-placental circulation and luteal phase support [8, 9].

Hence, the therapeutic application of progesterone during pregnancy, is targeted to the prevention and
treatment of threatened miscarriage, recurrent miscarriage and preterm birth.

**Immunological factors and role in implantation**

For the maternal immune system, the fetus is recognized as a semi-allograft. Maternal immune response, in fact, has a key role not only during the implantation process but also in the maintenance of early pregnancy. The maternal immune cells do not attack and reject a fetus during the pregnancy period. The immune tolerance is established in the maternal decidua in a specific area defined as the feto-maternal interface. On the contrary, if there is an alteration of the complex local immune network and maternal immune cells recognize the fetus as not-self, the maternal immune cells will reject the embryo fetus leading to implantation failure and miscarriage will occur [10].

The association between pro-inflammatory cytokines and recurrent miscarriages may be due to an increase in cell-mediated immunoresponse with a low antibody production. On the one hand, Th1-type cytokines (IFN-γ, IL-2, TNF-α) promote allograft rejection and compromise pregnancy; on the other hand, Th2-type cytokines (IL-3, IL-4, IL-5, IL-10, TGF-β2), by inhibiting Th1 response, promote allograft tolerance and therefore may improve fetal survival. On the basis of this mechanism, the aim of the therapy is to find ways to downregulate pro-inflammatory cytokines and/or to upregulate anti-inflammatory cytokines [10]. Several immunological effects of progesterone are mediated by an immunomodulatory molecule secreted by pregnancy lymphocytes so-called progesterone-induced blocking factor (PIBF), a protein with inhibitory effects on cell-mediated immune reactions [11, 12]. In this perspective, natural micronized progesterone and dydrogesterone are interesting therapeutic agents for the modulation of the effects that pro-inflammatory and anti-inflammatory cytokines have on the fetus and placenta [13]. The presence of progesterone and its interaction with progesterone receptors at the decidua level appears to play a major role in the maternal defense strategy [2]. It induces an important suppression of T-cell reactions, inhibits NK cells and exerts a synergistic action with Pg E2 [14, 15] (Figure 1).

**Figure 1:** The pivotal role of progesterone receptor-mediated immunomodulation in successful pregnancy.
LAK cells, Lymphokine activated killer cell; NK, natural killer cells; PBMC, peripheral blood mononuclear cells.
Luteal deficiency

A defect in corpus luteum function is associated both with implantation failure and miscarriage. Before the placenta starts producing progesterone, in fact, the corpus luteum production has to support the early pregnancy [16].

It has been demonstrated that progesterone may promote the invasion of extravillous trophoblasts to the decidua by inhibiting apoptosis of extravillous trophoblasts [8], confirming its rational use for luteal-phase support. In assisted reproductive cycles progesterone supplementation is recommended after ovum pick up when it is not sufficiently produced in early implantation [17, 18].

Role in myometrial contractility

Regarding the myometrial effect, progesterone has been shown to possess tocolytic action on the myometrium both in vitro and in vivo during pregnancy [19, 20].

It has been demonstrated that adequate progesterone concentrations in myometrium are able to counteract prostaglandin stimulatory activity as well as oxytocin. Progesterone decreases the concentration of myometrial oxytocin receptors, which counteract the effect of estrogens. The same is true with respect to the number and properties of gap junctions [21]. Moreover, progesterone and its metabolites induce uterine quiescence through interactions between nuclear and membrane progesterone receptors [6, 22, 23].

Progesterone has also been shown in vivo to be concentration dependent. Only high-dosage progesterone exerts a tocolytic action in early pregnancy. 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) [21].

It has been demonstrated, instead, that 17α-hydroxyprogesterone caproate (17 OHP-C) does not directly inhibit human myometrial contractions in vitro. Ruddock et al., in fact, showed that surprisingly 17 OHP-C dose dependently is able to stimulate contractility [24].

Since the 1990s, progesterone has been studied for its possible role in preterm birth. Keirse in his meta-analysis of placebo-controlled trials, investigated the possible prophylactic use of a synthetic progestogen (17 OHP-C) in women at high risk. This analysis demonstrated that this kind of progesterone offered no support against miscarriage, but it demonstrated the reduction of the occurrence of preterm birth and of the rate of low birth weight babies [25]. Although the pharmacokinetics and pharmacodynamics of natural progesterone have been well studied since 1935 when it has been synthesized, its use in the pathophysiology of pregnancy remains controversial. One of these concerns is the route of administration [26].

Key differences in the route of administration

Once the therapeutic need of progesterone is established, the key factor is the decision for the best route to administer the hormone and the optimal dosage determination.

The modality of absorption derives from: the pharmaceutical form used, the blood flow existing in the site of administration, the solubility in tissues in which the drug is placed.

Progesterone can be administered by many different routes, but the most utilized are oral, vaginal and intramuscular administration (Table 1).

Even if oral administration guarantees optimal compliance by patients, it may show several disadvantages, depending on the targeted indication, the main being its poor bioavailability and rapid metabolism with high variability in the plasma concentration mainly due to inter-individual variability in gastric filling and enteropathic circulation. The oral administration also shows major shortcoming when used during pregnancy: i.e. metabolites produced during liver passage that could interfere with specific progesterone action and discrepancy between progesterone blood levels and endometrial histology in controlled stimulated cycles in assisted reproductive technology (ART) [27, 28].

A number of synthetic oral progestogens including dydrogesterone have been developed to overcome progesterone’s variability in bioavailability. Their biological activities and receptor-binding affinities, however, differ from natural micronized progesterone and may result in different pharmacodynamics and pharmacological effects, such as increased androgenic effects, fluid retention, alterations in high density lipoproteins, acne, weight gain, headaches, mood disturbances, and possible mutagenicity or teratogenicity (Table 2).

The oral route for progesterone may also result in unwanted side effects such as nausea, headache and sleepiness. To improve the characteristics of oral administration, micronization of progesterone manufactured by hemi-synthesis from a plant source (i.e. Mexican wild yams, Dioscorea barbasco), has been formulated in an oil substrate yet the molecular structure of progesterone is exactly "body-identical" to endogenous human
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Table 1: Routes of administration of progesterone.

<table>
<thead>
<tr>
<th>Different routes of administration</th>
<th>Different pharmacokinetics and dynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular</td>
<td>Supraphysiological plasma concentrations</td>
</tr>
<tr>
<td>– Peaks and valleys</td>
<td>– Possible allergic reactions</td>
</tr>
<tr>
<td>Oral</td>
<td>– High interindividual variability in plasma concentrations</td>
</tr>
<tr>
<td>– Rapid increase in plasma concentration followed by a gradual decrease</td>
<td></td>
</tr>
<tr>
<td>– First liver pass effect with several biological active metabolites</td>
<td></td>
</tr>
<tr>
<td>– Specific activity on different target organs (uterus, brain...)</td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>– Stable plasma concentrations and consistent tissue levels</td>
</tr>
<tr>
<td>– First uterine pass effect with targeted delivery into the endometrium</td>
<td></td>
</tr>
<tr>
<td>– Mimics more physiological form of endometrium transformation</td>
<td></td>
</tr>
<tr>
<td>– Minimal adverse effects</td>
<td>Metabolization</td>
</tr>
<tr>
<td></td>
<td>– in the gut (bacteria with 5b-reductase activity)</td>
</tr>
<tr>
<td></td>
<td>– in the intestinal wall (5a-reductase activity)</td>
</tr>
<tr>
<td></td>
<td>– in the liver (5b-reductase, 3a- and 20a-hydrodylase activities)</td>
</tr>
<tr>
<td></td>
<td>– normal vaginal bacteria and mucosa seem devoid of 5a- and 5b-reductases</td>
</tr>
<tr>
<td></td>
<td>– after vaginal, only a small increase in 5a-pregnanolone observed and 5b-pregnanolone levels were not affected</td>
</tr>
</tbody>
</table>

Table 2: Biological activities of natural progesterone versus synthetic progestins.

<table>
<thead>
<tr>
<th></th>
<th>PR</th>
<th>Anti-E</th>
<th>ER</th>
<th>AR</th>
<th>Anti-A</th>
<th>Anti-mineral</th>
<th>GABAα</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>-</td>
</tr>
<tr>
<td>Dydrogesterone</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>±</td>
<td>-</td>
</tr>
<tr>
<td>MPA</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LNG</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Adapted from Schindler et al., Kuhl, Barentsen et al. [29–31].

Micronization of progesterone in particle sizes of <10 μm extensively increases the available surface area of the drug and enhances the aqueous dissolution rate and intestinal absorption of progesterone. Suspension in oil packaged in a gelatin soft capsule has been shown to further enhance the intestinal absorption of micronized progesterone [33].

The vaginal route results in higher concentrations in the uterus [21, 26]. Bulletti et al. documented the hypothesis of a “first uterine pass effect”, suggested by the evidence of higher than expected uterine tissue concentrations after vaginal administration of progesterone. Three different hypotheses have been reported to explain the first uterine pass: direct diffusion through or between cells from the vagina to the uterus, portal-like arrangements of lymphatics linking the upper vagina to the uterus, a counter occurrence circulation system, much like a portal system, with vein to artery diffusion between the upper vagina and the uterus. They demonstrated that a “first uterine pass effect” occurs when a drug is delivered vaginally, confirming that the vaginal route permits targeted drug delivery to the uterus, maximizing the desired effects while minimizing the potential for adverse systemic effects [34, 35] (Figure 2).

Endometrial progesterone concentrations were higher with vaginally administered progesterone than endometrial concentrations observed in women with normal ovulation exceeding by more than 10-folds the levels achieved by systemic administration; but supraphysiologic plasma level was reached after intramuscular administration, about seven times higher than after vaginal administration. The time to peak concentration is generally slightly lower than after administration of the oral micronized preparation. Moreover, after vaginal administration, plasma concentrations display a plateau-like profile, with a more constant concentration over time. Peak plasma levels of progesterone obtained appear to be variable and not consistently greater or less than corresponding peak plasma values obtained after oral administration of micronized progesterone [33]. Cicinelli et al. demonstrated in a randomized open study the direct transport of progesterone from vagina to uterus comparing progesterone concentrations in serum and endometrial tissue from hysterectomy specimens after vaginal or intramuscular administration of progesterone. The ratios of endometrial to serum progesterone concentrations were markedly higher in women who received vaginal progesterone [36].

Historically, the most common delivery method of progesterone has been through the intramuscular route [33]. However, progesterone administered intramuscularly cannot be applied by the patient herself (it requires assistance from a nurse), can provide local discomfort (painful injection, redness, non-septic abscesses at the injection site) and may rarely induce acute eosinophilic pneumonia [37] but it is the route that results in the highest blood
levels, that can be administered to a patient with vaginal bleeding and needs only one single daily dose [21, 26].

Others routes of administration have been suggested [38]. Several formulations of transdermal progesterone including patches, gels and creams that can effectively penetrate the skin have been proposed but there is insufficient evidence from scientific studies to substantiate the transdermal application of progesterone when systemic luteal phase blood levels are mandatory such as in pregnancy maintenance. Even if those preparations are not known to pose any risks to health, it is noteworthy, in fact, that progesterone is rapidly metabolized by the 5-α-reductase enzyme present in the skin, which converts it to 5-α-dihydro-progesterone, thereby lowering plasma progesterone levels. Lastly, the use of rectal administration, provides wide variability absorption and moreover there is insufficient scientific clinical evidence concerning this route of administration and its effects on the endometrium [39]. Moreover the prevalence of tenesmus (35.1 vs. 21.1%) and rectal itching (26.7 vs. 2.8%) were more significant in the rectal route compared to the vaginal route of administration [40].

Main uses of progesterone

Threatened miscarriage

The various causes 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 or no treatment, and vaginal bleeding in early pregnancy is not synonymous with threatened miscarriage [26].

In many cases of miscarriage a causative factor may be an insufficient secretion of progesterone; consequently in these cases progestogens have been used, beginning from the first trimester of pregnancy, in order to prevent spontaneous miscarriage. Haas and Ramsey demonstrated that there is no evidence to support the routine use of progestogen to prevent miscarriage in early to mid-pregnancy; however, there seems to be evidence of benefit of this therapy in women with a history of recurrent miscarriage [41].

Sotiriadis et al. demonstrated in a review that, although bed rest and progesterone supplements are often advised, they do not seem to improve the outcome of women with a threatened abortion [42].

The lack of evidence regarding the use of progesterone, however, probably does not correspond to its lack of efficacy taking into consideration some convincing biological plausibility.

Through a randomized, parallel group, double-blind, double-dummy, controlled study, Czajkowski et al. studied the effect of progesterone on uteroplacental circulation in threatened abortions comparing a micronized vaginal progesterone formulation with oral dydrogesterone tablets. It showed that micronized vaginal progesterone, but not dydrogesterone, significantly decreased the spiral artery PI and RI, both markers of adequate uteroplacental circulation [9] (Figure 3).

Siew et al. in a recent parallel-group, open-label, randomized controlled trial, compared the change in serum progesterone and progesterone-induced blocking factor pretreatment and posttreatment (at day 4–6 of treatment)
in women with threatened miscarriage, who were randomized to receive micronized vaginal progesterone or oral dydrogesterone tablets. Micronized progesterone treatment led to a greater increase in serum progesterone and progesterone-induced blocking factor levels post-treatment. However, there was no significant difference in their clinical efficacy and the extent of bleeding at day 4–6 and subsequent miscarriage rates were comparable. Those results could be useful in early prognostication of treatment outcome [43].

An optimal strategy to face this situation is to encourage an appropriate diagnosis in order to apply a treatment aimed to the pathology. One possible way is to decrease or to stop uterine contraction. Progesterone has been shown to possess, only at high dosage, a tocolytic action in early pregnancy [21].

A recent meta-analysis of cohort studies suggested that a single progesterone measurement for women in early pregnancy presenting with bleeding or pain and inconclusive ultrasound assessments can rule out a viable pregnancy [44].

Finally, the authors of a recent Cochrane Database of Systematic Reviews suggested that progestogens are effective in the treatment of threatened miscarriage with no evidence of increased rates of pregnancy-induced hypertension or antepartum hemorrhage as harmful effects to the mother, nor increased occurrence of congenital abnormalities in the newborn. However, the analysis was limited by the small number and the poor methodological quality of eligible studies (four studies) and the small number of the participants (421), which limited the power of the meta-analysis and hence of this conclusion [45]. Moreover, a recent NICE guideline stated that a very large multicenter randomized controlled trial of women treated with either progesterone or placebo should be conducted. In this perspective, the on-going PRISM study in the UK, a large prospective double-blind placebo randomized clinical trial sufficiently powered will determine the efficacy of vaginal micronized progesterone 400 mg BID supplementation in 4150 women presenting with vaginal bleeding and pain in the first 12 weeks of pregnancy in the prevention of threatened miscarriage.

Recurrent miscarriage

Recurrent miscarriage is defined as three consecutive pregnancy losses. Extensive investigation of the women involved will fail to find a recognizable cause in up to half of cases [21, 26].

The pathophysiology of recurrent miscarriage is complex and it includes anatomical, genetic and molecular abnormalities, endocrine disorders, thrombophilias and anti-phospholipid syndrome.

Luteal phase defects and immunotolerance derangements are the most common recognizable causes [21, 26].

Considerable evidence indicates that women with idiopathic recurrent miscarriage may benefit from progestogen treatment, as it has been shown to be an essential immunomodulatory agent in early pregnancy.

Walch et al. demonstrated that dydrogesterone given orally during the first trimester of pregnancy in women suffering from recurrent miscarriage can induce immunomodulation and improve pregnancy outcome [46].

Also other studies have shown that the progestogen supplementation can potentially provide a treatment option for those patients. The progesterone role is probably exerted in the expression, modulation and inhibition of various growth factors, cytokines, cell adhesion molecules decidual proteins [47].

We tested the role of micronized progesterone in recurrent miscarriages (women with 2 or >2 abortions) comparing women with positive or negative anamnesis for autoimmunity (for different types of autoantibodies but...
especially thyroid autoantibodies) treated with no drugs, acetyl-salicylic acid (ASA) 100 mg/day alone or in association with micronized progesterone 200 mg/day. Results showed that the group of women with proven autoimmunity treated with ASA and progesterone had the same outcomes (live birth rate at term) as the group with autoimmunity not proven treated only with aspirin (Figure 4).

In a recent multicenter, double-blind, placebo-controlled, randomized trial, it was discussed whether progesterone supplementation in the first trimester of pregnancy could increase the rate of live births among women with unexplained recurrent miscarriage. The treatment consisted in vaginal micronized progesterone 400 mg twice-daily or placebo, from a time soon after a positive urinary pregnancy test, no later than 6 weeks of gestation, through 12 week of gestation. They demonstrated that in women with a history of unexplained recurrent miscarriages, progesterone therapy in the first trimester of pregnancy does not result in a significantly high rate of births beyond 24 weeks. However, a secondary outcome demonstrated that vaginal progesterone was safe for the mother and the fetus, due to no statistical significant difference in frequency of adverse events between treatment and placebo [48] (Tables 3 and 4).

As the authors mention in the discussion of the publication, there are some limitations in this study. Progesterone treatment was initiated only after a urinary pregnancy test was confirmed, for a duration limited to 12 weeks of pregnancy, and for some patients taking the progesterone treatment for a very short period of time and thus this study result cannot address, as to whether progesterone supplementation should be more effective in reducing the risk of miscarriage if administered during the luteal phase of the cycle, before confirmation of pregnancy and/or after week 12 of pregnancy. However, this the first well-designed randomized controlled trial with live birth rate as the primary outcome, different from relative risk of miscarriage outcome in previous studies with progesterone [49] or dydrogesterone [50].

Figure 4: Use of progesterone in recurrent miscarriages.

Table 3: Primary outcome and secondary outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No./total no. (%)</th>
<th>Progesterone</th>
<th>Placebo</th>
<th>Relative risk (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical pregnancy at 6–8 weeks</td>
<td>326/398 (81.9)</td>
<td>334/428 (78.0)</td>
<td>1.05 (0.98–1.12)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Ongoing pregnancy at 12 weeks</td>
<td>267/398 (67.1)</td>
<td>277/428 (64.7)</td>
<td>1.04 (0.94–1.14)</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>6/398 (1.5)</td>
<td>7/428 (1.6)</td>
<td>0.92 (0.31–2.72)</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>Miscarriage</td>
<td>128/398 (32.2)</td>
<td>143/428 (33.4)</td>
<td>0.96 (0.79–1.17)</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Stillbirth</td>
<td>1/398 (0.3)</td>
<td>2/428 (0.5)</td>
<td>0.54 (0.05–5.92)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>Live birth after 24 weeks 0 days of gestation</td>
<td>262/398 (65.8)</td>
<td>271/428 (63.3)</td>
<td>1.04 (0.94–1.15)</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Twin live births after 24 weeks 0 days of gestation</td>
<td>4/398 (1.0)</td>
<td>5/428 (1.2)</td>
<td>0.86 (0.23–3.18)</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Gestation outcomes among women with live births</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live birth before 28 weeks 0 days of gestation</td>
<td>1/262 (0.4)</td>
<td>1/271 (0.4)</td>
<td>1.03 (0.06–16.49)</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Live birth before 34 weeks 0 days of gestation</td>
<td>10/262 (3.8)</td>
<td>10/271 (3.7)</td>
<td>1.03 (0.44–2.45)</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>Live birth before 37 weeks 0 days of gestation</td>
<td>27/262 (10.3)</td>
<td>25/271 (9.2)</td>
<td>1.12 (0.67–1.87)</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Neonatal outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any congenital anomaly</td>
<td>8/266 (3.0)</td>
<td>11/276 (4.0)</td>
<td>0.75 (0.31–1.85)</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Genital congenital anomaly</td>
<td>1/266 (0.4)</td>
<td>1/276 (0.4)</td>
<td>1.04 (0.07–16.50)</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Newborn survival to 28 days</td>
<td>260/261 (99.6)</td>
<td>269/269 (100)</td>
<td>1.00 (0.99–1.00)</td>
<td>0.32</td>
<td></td>
</tr>
</tbody>
</table>

*The median gestational age at miscarriage was 7.3 weeks (interquartile range, 6.0–8.7) in the progesterone group and 7.1 weeks (interquartile range, 6.0–8.5) in the placebo group (relative risk, 0.0; 95% CI, –0.6 to 0.4; p = 0.87). *The end point is listed per trial participant. *The end point is listed per neonate. From Coomarasamy et al. [48].
Preterm birth is the leading cause of perinatal mortality and morbidity. Its incidence has not declined (12% of all births) and, due to its long-term neuro-developmental sequelae, it is one of the major expenses on health and educational resources [51–53]. The mechanism of human parturition is the expression of anatomic, biochemical, physiologic and clinical events that occur in the mother and in the fetus in both term and preterm labor. This pathway consists of:

- decidual/fetal membrane activation
- increased uterine contractility
- cervical ripening (dilatation and effacement).

Preterm labor is the consequence of the pathologic activation of one or more of those elements (Figure 5).

The apparent loss of progesterone sensitivity at term could be a consequence of several different mechanisms including: alterations in progesterone receptors (PR) isoform ratios anti-inflammatory function of progesterone, the catabolism of progesterone in the uterus into inactive compounds, changes in cofactor protein levels affecting PR transactivation and inflammation-induced trans-repression of PR [21].

Before undertaking any therapeutic strategy, careful identification is needed, so as to detect manageable conditions and fetal and/or maternal contraindications.

The real challenge is to develop sensitive and specific tests that reliably detect these pregnancy’s changes before they became irreversible and to find effective intervention of arresting the process of preterm labor to enhance the effectiveness of current available interventions.

Regarding the management of threatened preterm labor, tocolysis and administration of corticosteroids to induce lung maturation are the first therapeutic tools; also bed rest and hydration are usually recommended in the management of these patients, although not proven to have a clear efficacy.

The tocolytic effect of oral micronized progesterone was already suggested in 1985 as reported by Erny et al.

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### Table 4: Vaginal progesterone in women with an asymptomatic short cervix in the midtrimester ultrasound decreases PTD and improves neonatal outcome.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of trials</th>
<th>No. of events/total no.</th>
<th>Pooled RR (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaginal progesterone</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm birth &lt;37 week</td>
<td>5</td>
<td>144/388</td>
<td>165/387</td>
<td>0.89 (0.75–1.06)</td>
</tr>
<tr>
<td>Preterm birth &lt;36 week</td>
<td>5</td>
<td>108/388</td>
<td>136/387</td>
<td>0.82 (0.67–1.00)</td>
</tr>
<tr>
<td>Preterm birth &lt;35 week</td>
<td>5</td>
<td>79/388</td>
<td>118/387</td>
<td>0.69 (0.55–0.88)</td>
</tr>
<tr>
<td>Preterm birth &lt;34 week</td>
<td>5</td>
<td>62/388</td>
<td>105/387</td>
<td>0.61 (0.47–0.81)</td>
</tr>
<tr>
<td>Preterm birth &lt;30 week</td>
<td>5</td>
<td>29/388</td>
<td>51/387</td>
<td>0.58 (0.38–0.89)</td>
</tr>
<tr>
<td>Preterm birth &lt;28 week</td>
<td>5</td>
<td>21/388</td>
<td>43/387</td>
<td>0.50 (0.30–0.81)</td>
</tr>
<tr>
<td>Spontaneous preterm birth &lt;33 week</td>
<td>5</td>
<td>39/388</td>
<td>71/387</td>
<td>0.57 (0.40–0.81)</td>
</tr>
<tr>
<td>Spontaneous preterm birth &lt;34 week</td>
<td>5</td>
<td>51/388</td>
<td>87/387</td>
<td>0.62 (0.46–0.84)</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>5</td>
<td>25/411</td>
<td>52/416</td>
<td>0.48 (0.30–0.76)</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>5</td>
<td>8/411</td>
<td>15/416</td>
<td>0.55 (0.26–1.19)</td>
</tr>
<tr>
<td>Admission to NICU</td>
<td>5</td>
<td>85/411</td>
<td>121/416</td>
<td>0.75 (0.59–0.94)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>5</td>
<td>35/411</td>
<td>51/416</td>
<td>0.66 (0.44–0.98)</td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>7</td>
<td>30/1967</td>
<td>34/1954</td>
<td>0.89 (0.55–1.44)</td>
</tr>
<tr>
<td>Any maternal adverse event</td>
<td>3</td>
<td>86/624</td>
<td>80/595</td>
<td>1.04 (0.79–1.38)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>5</td>
<td>6/411</td>
<td>9/416</td>
<td>0.74 (0.27–2.05)</td>
</tr>
</tbody>
</table>

Adapted from Romero et al. [59].

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**Figure 5:** Labor, term and preterm, is characterized by increased myometrial contractility, cervical dilatation and rupture of the chorionamniotic membranes.

Adapted from Romero et al. [54].
These investigators evaluated the effects of 400 mg of orally absorbed micronized progesterone or placebo in women at risk for premature labor; 88% of the patients who were treated with oral micronized progesterone had decreased uterine activity compared with 42% of the patients who received placebo [33].

In a recent FIGO Committee Report it has been established that the prevention of preterm birth should be based on the use of cervical length and the progesterone. It has been recommended, in fact to screen the sonographic cervical length in all women at 19–23 6/7 weeks using transvaginal ultrasound and treatment with daily vaginal progesterone in cases of cervical length ≤25 mm. It has been studied as a cost-effective model for the prevention of preterm birth [55].

Vaginal micronized progesterone and related synthetic compounds such as 17 OHP-C injections, as well as others progestogens, have been tested in clinical trials for the prevention of preterm birth [56], especially on the three main groups of patients considered at particularly high risk:
- patients with a history of spontaneous preterm birth,
- patients with a short cervix,
- patients with multiple pregnancies.

Studies using synthetic progesterone to reduce the rate of preterm delivery have been reported with mixed results, more especially with 17 OHP-C injections in women at risk for preterm birth with a short cervix [57], while women assuming natural progesterone demonstrated more consistently benefits in view of efficacy, cost-effectiveness, availability and biological safety in mothers and their children [1, 57].

No other progestagens have been so far used in the management of preterm labor and birth.

The vast majority of clinical trials were performed with various formulations of either vaginal micronized progesterone vaginally applied and 17 OHP-C weekly intramuscular injections. The use of both vaginal micronized progesterone and 17 OHP-C intramuscular injections was advised in asymptomatic women at risk with prior history of preterm birth as an early prophylaxis of preterm birth, but only vaginal micronized progesterone was recommended in single pregnant, nulliparous women with a silent cervical shortening (<25 mm) detected with transvaginal ultrasound at midgestation.

Furthermore Istwan et al. demonstrated that in patients with a history of one prior spontaneous preterm delivery receiving prophylactic 17 OHP-C, but not in patients with more than one prior spontaneous preterm delivery, a previous term delivery confers a reduction in risk [58].

One of the first well-designed study concerning the prophylactic use of vaginal progesterone to decrease the rate of preterm birth in patient at high risk (at least one previous spontaneous preterm birth, prophylactic cervical cerclage, uterine malformation) has been performed by Fonseca et al. They demonstrated that the daily use of 100 mg vaginal progesterone in these women is able to reduce the frequency of uterine contractions and the rate of preterm birth [59].

More recently it has also been demonstrated, based on a systematic review of five randomized controlled trials and a meta-analysis of individual patient data that the use of vaginal micronized progesterone in asymptomatic women with a sonographic short cervix not only reduces the risk of preterm birth, but it is also able to reduce neonatal morbidity and mortality (Figure 6, Table 4) [60].

In nulliparous women with a midtrimester cervical length <30 mm, the use of weekly intramuscular 17 OHP-C was not shown to reduce the frequency of preterm birth [61].

Comparing the use of vaginal micronized progesterone with the intramuscular administration of 17 OHP-C, it also demonstrated a statistically significant decrease in severe side effects and the number of admissions to the Neonatal Intensive Care Unit in the vaginal progesterone group [62].

It has also been studied if maternal weight and body mass index (BMI) modifies the effectiveness of 17 OHP-C in preventing preterm birth. It resulted that both maternal weight and BMI reduced the effectiveness of this treatment due to subtherapeutic serum levels in those patients [63].

In either twins or triplets, neither vaginal micronized progesterone nor 17 OHP-C are able to prevent preterm birth [56]. Already in 1980, Hartikainen-Sorri et al. treated 77 twin pregnancies during the last trimester until the 37th gestational week with weekly injections of either 17 OHP-C or a placebo, showing no differences in the gestational length, birth weight and outcome of the neonates [64]. Cooms et al. demonstrated that nowadays the prophylactic administration of 17 OH-C to mother with twin pregnancy does not reduce the rate of preterm delivery or neonatal morbidity [65]. A recent individual participant data meta-analysis (IPDMA) of 13 eligible RCTs, in unselected women with an uncomplicated twin gestation, treatment with progestogens (intramuscular 17Pc or vaginal natural progesterone) did not improve the perinatal outcome. However, vaginal micronized progesterone may be effective in the reduction of adverse perinatal outcome in women with a cervical length of ≤25 mm; further research is warranted to confirm this finding [66].

It has recently been demonstrated that the possible effect of vaginal progesterone, but not of 17 OHP-C, in the
prevention on preterm birth is related to its immunomodulatory functions. Furcron et al. studied the local effects of vaginal progesterone and 17 OHP-C on adaptive and innate immune cells implicated in the process of parturition in the murine maternal-fetal interface. They showed that only vaginal progesterone exerts local anti-inflammatory effects at the maternal-fetal interface and the cervix protecting against endotoxin-induced preterm birth [67].

The use of vaginal progesterone has also been proposed in combination with cervical pessary; in a recent study, Stricker et al. compared two groups of at-risk patients and screening patients treated with a cervical pessary alone to patients treated with a pessary plus vaginal micronized progesterone.

Treatment of precocious cervical ripening with a cervical pessary plus vaginal progesterone did not reduce the rates of preterm delivery compared to a pessary alone. However, the neonatal intensive care utilization was shorter in patients who received additional vaginal progesterone although there was no difference in composite poor neonatal outcome [68].

The administration of high-dosage progesterone has been advocated as a possible tocolytic agent.

Natural progesterone has documented properties of inhibiting uterine contractions, whereas 17 OHP-C seems to have no effect on uterine contractions [56]. The action of progesterone is slow and it can be used for acute tocolysis only in conjunction with acute tocolytic agents such as β-agonists [69]. 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 [21, 26] (Table 5).

A recent study of Baumbach et al. demonstrates that progesterone significantly inhibits uterine contractility at relatively high concentration and its combination with nifedipine and indomethacin increases this effect [70] (Figure 7).

Also Chanrachakul et al. recently demonstrated this synergetic effect of progesterone with β-mimetics. They concluded that natural progesterone is able to increase the relaxant effect of ritodrine, most likely through non-genic action [51]. This was also suggested previously by Noblot et al. [71].

Progesterone can be taken into consideration for the maintenance of uterine quiescence in the case of patients already treated for an episode of threatened preterm labor. In comparison with nifedipine, progesterone has a significantly higher role in prolonging pregnancies of women with arrested preterm labor and, moreover, it results in a better neonatal outcome with lesser side effects [52]. In a recent meta-analysis of randomized controlled trials the efficacy of maintenance tocolysis with vaginal micronized progesterone compared to placebo or no treatment in singleton gestation with arrested preterm labor was evaluated. Suhag et al., suggested that maintenance tocolysis with vaginal micronized progesterone is associated with prevention of preterm birth, significant prolongation of pregnancy and lower neonatal sepsis [72]. Borna et al. also studied the role of progesterone in the maintenance of tocolysis after threatened preterm labor treated with intravenous

![Figure 6: Vaginal progesterone and reduction of preterm birth before 33 weeks of gestation. From Romero et al. [59].](image)
magnesium sulfate. They found a longer latency until delivery and better gestational age at delivery and low birth weight [73]. Moreover there is evidence that the only use of micronized progesterone reduced the rate of preterm birth in women successfully treated for a preterm labor episode, despite some negative existing trials [56, 74]. In conclusion, natural “body-identical” progesterone is a molecule extensively and well-studied and nowadays more evaluated than before. According to guidelines published in the recent years by different societies [the International Federation of Gynecology and Obstetrics (FIGO), The Royal College of Obstetricians and Gynaecologists (RCOG), the American Congress of Obstetricians and Gynecologists (ACOG), the European Association of Perinatal Medicine (EAPM) and the Society of Obstetricians and Gynaecologists of Canada (SOGC)] concerning the management of preterm labor, the use of progesterone can be recommended as follows:

- early prophylaxis (from 12 to 36 weeks of gestation) with either micronized P4 (200 mg vaginally daily) or 17 OHP-C (injection of 250 mg weekly) to prevent recurrence in the case of prior history of PTB [55, 74, 75];
- vaginal micronized progesterone in singleton gestation, with and without history of prior PTB, with short cervical length (<25 mm) at 18–23 weeks of gestation, as it has been found to be associated with reduction in the rate of PTB and perinatal morbidity and mortality (200 mg vaginal daily) [54, 55, 75];
- in nulliparous women in single pregnant women successfully treated for a PTL as maintenance tocolysis, (400 mg vaginal progesterone), but further studies may be required to optimize the daily dosage [54, 55]
- use of vaginal progesterone in acute tocolysis (400 mg vaginal daily for 48 h) in association with drugs usually utilized for tocolysis.

### Table 5: Use of progesterone in association with tocolytic agents.

<table>
<thead>
<tr>
<th>Patients</th>
<th>47</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age</td>
<td>30.5 ws</td>
<td>30.3 ws</td>
</tr>
<tr>
<td>Treatment</td>
<td>- Ritodrine (100 mg in saline 0.1–0.3 mg/min)</td>
<td>- Ritodrine (50 mg in saline 0.1–0.3 mg/min)</td>
</tr>
<tr>
<td>- Progesterone (200 mg die)</td>
<td>- Progesterone (200 mg die)</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>- Deliveries after 48 h: 87%</td>
<td>- Deliveries after 48 h: 85%</td>
</tr>
<tr>
<td>- Deliveries after 7 days: 65%</td>
<td>- Deliveries after 7 days: 68%</td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>- Mat. tachycardia: 97%</td>
<td>- Mat tachycardia: 42%</td>
</tr>
<tr>
<td>- Nausea and vomiting: 28%</td>
<td>- Nausea and vomiting: 6%</td>
<td></td>
</tr>
<tr>
<td>- Tremblings: 26%</td>
<td>- Tremblings: 12%</td>
<td></td>
</tr>
<tr>
<td>- Palpitations: 32%</td>
<td>- Palpitations: 12%</td>
<td></td>
</tr>
<tr>
<td>- Chest pain: 15%</td>
<td>- Chest pain: 8%</td>
<td></td>
</tr>
<tr>
<td>- Hyperglycemia: 47%</td>
<td>- Hyperglycemia: 28%</td>
<td></td>
</tr>
<tr>
<td>- Hypokaliemia: 92%</td>
<td>- Hypokaliemia: 23%</td>
<td></td>
</tr>
</tbody>
</table>

Modified from Di Renzo et al. [26].
References


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