The Use of Progesterone in Clinical Practice: Evaluation of its Efficacy in Diverse Indications Using Different Routes of Administration

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Abstract: *Introduction:* Progesterone is a hormone of paramount importance in the reproductive physiology. Its multiple physiological roles and pharmacology have been extensively studied throughout the years. However, the use of progesterone in the pathophysiology of pregnancy as well as in its other indications remains arguable for diverse reasons. One of these reasons concerns the fact that there have been few large randomised controlled trials, which are not easily comparable because of the different dosages, populations and routes of administration used. Regarding this last issue, the route of progesterone administration may have a strong influence on the efficacy of the treatment since the distribution and concentration of the hormone at the tissutal level varies considerably.

Objective: To review the literature concerning the efficacy of progesterone in its diverse indications in correlation to the different routes of administration used.

Methods: The search strategy included a literature search of PubMed, MEDLINE and the Cochrane Database from 1949 to April 2005, as well as a review of reference lists of identified studies and a hand search of relevant textbooks and reference works. Search terms used included: progesterone, pregnancy, preterm birth, preterm labor, threatened miscarriage, recurrent miscarriage, menopause, contraception, pharmacology, route of administration. Study designs included experimental studies, observational studies, case control studies, reviews, letters, and editorials.

Results: The search on MEDLINE identified approximately 3800 articles. We found only limited literature relating to some of the administration route of progesterone (transnasal, transdermic, sublingual, rectal).

Conclusion: Many routes of progesterone administration have been studied, but the only routes of administration used in the clinical practice are the i.m., oral and vaginal one. Among these options, the intramuscular administration is the only one that ensures adequate and verifiable plasmatic levels of progesterone.

Key Words: Progesterone, routes of administration, pharmacokinetics, pharmacology.

INTRODUCTION

Progesterone is a hormone of paramount importance in reproductive physiology. The multiple physiological roles of progesterone, together with its pharmacokinetics have been deeply investigated through the year since its identification and synthesis in 1934. It is well known that progesterone is indispensable for pregnancy maintenance and also regulates the menstrual cycle and implantation. Its therapeutic use has been proposed and applied in the treatment of many gynaecological pathologies such as amenorrhoea, dysfunctional uterine bleeding, premenstrual syndrome, endometrial hyperplasia as well as in the pathophysiology of pregnancy. Furthermore progesterone has been used as a contraceptive, alone or in combination with an oestrogen, and as hormonal support in luteal phase deficiency in assisted reproduction [1].

Notwithstanding these premises, the use of progesterone in the pathophysiology of pregnancy and in the other indications of gynaecological practice (menstruation disturbances, premenstrual syndrome, postpartum depression, etc.) remains arguable for diverse reasons. One of these reasons concerns few large randomised controlled trials performed, which are not easily comparable because of the different dosages [2,3], populations and routes of administration used. Regarding this last issue, the route of progesterone administration may have a strong influence on the efficacy of the treatment since the distribution and concentration of the hormone at the tissutal level varies considerably. Consequently, choosing the proper route of administration is an important aspect of the therapeutic approach. Moreover, since progestogens are often associated with undesirable side effects, improved formulations and modes of progesterone administration continue to be currently under investigation, especially in HRT and contraception, in order to find an optimal therapeutic agent [4-6].

The aim of this study was to review the literature concerning the efficacy of progesterone in its diverse indications in correlation to the different routes of administration used. The search strategy included a literature search of PubMed, MEDLINE and the Cochrane Database from 1949 to April 2005, as well as a review of reference lists of identified studies and a hand search of relevant textbooks and reference works. Search terms used included

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the following key words: progesterone, pregnancy, preterm birth, preterm labor, threatened miscarriage, recurrent miscarriage, menopause, contraception, pharmacology, route of administration. Study designs included experimental studies, observational studies, case control studies, reviews, letters, and editorials. After a brief description of some important aspect of progesterone pharmacology, the literature dealing with the use of progesterone in different routes of administration is summarized in an attempt to more precisely define the features of progesterone treatment.

GENERAL PHARMACOLOGY OF PROGESTERONE

Progesterone represents an essential metabolic step in the biosynthesis of numerous steroids that include some glucocorticoids and mineralcorticoids. The transformation of exogenous progesterone in other hormones with different biological activity appears as a limit in clinical practice. Progesterone may be converted in desoxycorticosterone at peripheral tissue level. Extra-surrenalic synthesis of these strong mineralcorticoid from endogenous and exogenous progesterone has been highlighted [7-9]. Progesterone is largely metabolized at the intestinal and hepatic level by the reduction of the 3 and 20 hydroxyl groups, the reduction of the 4-5 double bond, by the hydroxylation at 16, 21 carbon and by conjugation with glucuronic and sulphuric acids [10].

Progesterone may compete with mineralcorticoids at the receptorial level therefore acting as a mineralcorticoids antagonist [11-13]. Moreover, a significant amount of progesterone is converted in desoxycorticosterone [9]. In women of the reproductive age, during the menstrual cycle, progesterone and desoxycorticosterone levels rise simultaneously reaching their maximum concentration during the luteal phase [7]. In women during the follicular phase circulating desoxycorticosterone is produced by the adrenal cortex. In opposition, during the luteal phase more than 75% of the circulating desoxycorticosterone comes from the peripheral conversion of progesterone at renal and aortic level [7,8].

The administration of exogenous progesterone is followed by a rapid increase of desoxycorticosterone plasmatic levels. Additionally, the route of progesterone administration may influence progesterone/desoxycorticosterone ratio. The effects of mineralcorticoids and of desoxycorticosterone are partially antagonized by the antimineralcorticoid effects of progesterone alone. One may theorize that a few clinical manifestations, i.e. the premenstrual syndrome, the gravidic oedema as well as the hypertensive disorders in pregnancy could be connected to the alterations of the progesterone/ desoxycorticosterone ratio.

ROUTES OF PROGESTERONE ADMINISTRATION

Once the therapeutical need of progesterone is established, selecting the proper route of administration is one of the main concerns [14,15]. Ordinarily, the route of administration of a drug is selected by considering the anatomic, physiopathological and pharmacotherapeutic aspects of the drug administration [15,16] rather than those concerning compliance and practical features. There are three main items that determine the drug to be successfully absorbed from the administration site which are: 1) the pharmaceutical form (tablets, suppositories, gel, solution for injection, etc.); 2) the solubility of the drug at the tissue level; 3) the hematic flow present at the site of administration. As regards the route of administration of progesterone, all the possible administration routes have been used with distinct results.

Transdermic Progesterone

This route of administration may seem to be beneficial for the patient since it is easy to use and shows a good compliance to the patient. Nevertheless, it does not allow plasmatic levels of progesterone to achieve adequate concentrations. First, being progesterone a lipophilic compound, it is not efficiently absorbed by the skin [17]. Moreover, the daily production of progesterone is an average of 25 mg, and by selecting the transdermic administration one should use about half of the body as an absorbing surface [18].

Notwithstanding this premises, natural progesterone creams are gaining popularity as a possible treatment for menopausal symptoms in combination with estrogens. A recent study evaluated the systemic absorption of a combination of transdermal estrogen and a progesterone cream (40 mg progesterone/day over 48 weeks) [19]. As expected, a significant although low increase in the plasma levels of progesterone was seen after 12 weeks (median 2.5 nmol/l) and no further increase was noted in the remainder of the study period. The controversy concerning the progesterone transdermic administration in postmenopausal women is that serum progesterone levels achieved with progesterone creams are too low to have a secretory effect on the endometrium [20], although antiproliferative effects on the endometrium have been demonstrated even with low levels of circulating progesterone.

In fact, it is remarkable that despite the low serum progesterone levels achieved with the creams, salivary progesterone levels are very high, indicating that progesterone levels in serum do not necessarily reflect those in tissues. One explanation is that after absorption through the skin, the lipophilic ingredients of creams, including progesterone, may have a preference for concentrating in the fatty layer below the dermis. For the rapid uptake and release of steroids operated by red blood cells passing through capillaries, these cells may play an important role in transporting progesterone to salivary glands and other tissues including those of the endometrium. In conclusion, it is arguable that further study are needed to assess the efficacy and safety of progesterone by this route of administration and in this indication.

Rectal Progesterone

The rectum has a complex hematic and lymphatic vascularization. Since the rectal mucosa shows a great variability of absorption, it is not considered an important site for drug absorption [21]. Regardless it is also important to remember that many active components are absorbed by the rectal mucosa as other lipoproteic membranes [22]. In effect, non-ionic and lipophylic compounds are easily absorbed by the rectal mucosa [23]. Some authors actually state that drugs which are easily metabolized by the liver

may be more effective when administered by endorectal route [16,24].

Indeed, when the active component is absorbed in the lower portion of the rectum and throughout the inferior hemorrhoidal veins, it goes directly to the general circulation, bypassing the hepatic first-pass elimination. On the contrary, if the compound is absorbed by the superior rectal ampulla it will reach the portal circulation throughout the superior hemorrhoidal vein [15,24]. Although this route of progesterone administration does not have an adequate bibliographic support it is still used in some anglo-saxon countries for HRT (Hormone Replacement Therapy) when progesterone is administered in combination with estrogens. Progesterone's plasmatic peak is reached 8 hours after the administration and is followed by a gradual decline of the plasmatic levels. As mentioned earlier, there is a wide variability of absorption among patients that makes the hematic peaks range between 15 and 52 ng/ml after the administration of 100 mg of progesterone by rectal route [25].

Sublingual Progesterone

This route of progesterone administration is not commonly used. In fact, not many studies are found in International literatures that discuss this issue [26-28]. In 1996 Stovall and collaborators [26] used this route of progesterone administration for luteal phase support in patients undergoing embryo transfer. The authors demonstrated that after the application of 50 or 100 mg of progesterone dissolved in 1 ml of sublingual suspension the plasmatic peaks were reached in 30-60 minutes. Plasmatic levels were at an average of 17.61±3.78 ng/ml when 100 mg of progesterone was administered. Therefore in order to reach adequate plasmatic levels the administration had to be repeated 2-3 times during the day.

Preliminary data of the Iowa Assisted Reproduction Program showed that 400 mg of progesterone has to be administered sublingually every 8 hours to obtain plasmatic levels similar to those achieved with the i.m. administration of 100 mg/die of progesterone [29]. The sublingual administration of micronized progesterone and estradiol (200 mg and 1 mg daily respectively administered in two tablets) in HRT has been studied by Miller and collaborator [27]. The results of the study showed a decreases in serum and urine markers of bone metabolism, a prevention of bone loss and a slight increase in spine and hip bone mineral density after 12 moths. However, more studies are needed in order to evaluate the effectiveness of this route of administration.

Transnasal Progesterone

Nasal mucosa is a potential site for progesterone administration due to its high vascularization and to the presence of microvilli that considerably expand the absorbing area [30,31]. This route of progesterone administration was proposed by Steege in 1986 and in 1993 Cicinelli proposed progesterone administration through nasal spray [32-35]. Although the obtained plasmatic levels did not have a therapeutic effect in clinical obstetrics the result of this study was interesting. This route of administration could be a good option in HRT in menopause [36].

Intrauterine Progesterone

The first progesterone-releasing intrauterine system was made available more than 30 years ago [6,37,38]. It released 65 μg progesterone over a 24 h period, and was approved for contraception for 1 year. The mechanisms of action of progesterone administered by this route of administration are not completely clarified. However, it has been proved that the hormone exerts a local antiproliferative action on the endometrium which becomes unresponsive to estrogens without affecting the hypothalamic-pituitary-ovarian axis and consequently ovulation [39,40].

Progesterone-releasing intrauterine systems have also been used and found effective in menstrual disorders, that is to say menorrhagia [41-43] and functional dysmenorrhoea [44-45], with few associated adverse effects. Intrauterine devices containing progesterone may be particularly interesting in premenopause because they are effective in the treatment of endometrial hyperplasia [46]. It is evident that the intrauterine route of administration of progesterone cannot be used in obstetrics because it would act as a contraceptive [47,48]. On the contrary, intrauterine devices containing progesterone may be particularly interesting in climateric [49]. In fact the vagina may represent an alternative delivery site of sex steroids for menopausal women [50]. The new ring technology provides continuous and consistent delivery of steroids for up to 3 months. Rings rest on the pelvic floor muscles in a nearly horizontal position and are usually imperceptible.

Oral Progesterone

The oral route of administration offers a high compliance to the patient because of the feasibility of the administration. However, in the case of oral progesterone, it also presents evident disadvantages. First of all, there is a great variability of absorption caused by individual factors and gastric filling [51,52]. Furthermore, oral progesterone shows a poor bioavailability [53] and a rapid clearance rate [54]. In fact orally administered progesterone is absorbed at the intestinal level and then reaches the liver through the portal vein where it is rapidly converted in metabolites (first-pass effect).

At this point, important side-effects are a consequence of this enterohepatic passage, such as dizziness, sleepiness, nausea etc. [55], caused by the formation of these catabolites. Furthermore, the rapid metabolism of the hormone determines a rapid fall of its plasmatic levels. Consequently, it is indispensable to administer high and repeated dosages of progesterone during the day in order to have an effective therapeutic action [56,57]. On the other side, this rapid metabolism also determines a rise of the plasmatic levels of progesterone catabolites (see over).

As a consequence, the development of a drug containing a progesterone formulation, which is able to pass through the gastric barrier and release the active component at the intestinal level should be viewed as advantageous. The dosages could be lowered and side-effects would occur less

frequently. Recently an oral micronized preparation of progesterone has been available on the market that allows a higher absorption of the active component [53,58]. The production of micronized progesterone requires a transformation of the chemical compound into very thin powder which is subsequently suspended in an oil vector, a process that considerably increases the bioavailability of the hormone [59].

However, even after the micronization of the active component, the intestinal absorption of progesterone is still limited. In addition there is still a considerable intersubject variability in the extent of progesterone absorbed [51,52]. In conclusion, even if the absorption of micronized progesterone resulted enhanced double in the presence of food, its bioavailability was approximately still 10% in comparison with intramuscular progesterone [53].

Some important consideration may be done analyzing the studies in which oral micronized progesterone has been administered in IVF for luteal phase support. Results showed that there was a significantly lower implantation rate per embryo compared to i.m. progesterone in luteal phase support in IVF cycles [60,61], in spite of the fact that circulating levels of progesterone were similar in both groups. Scarce results in terms of pregnancy and implantation rate have been reached by Buvat and collaborators [62]. In fact in their study the use of oral micronized progesterone in oil (100 mg at 8 am, 100 mg at 12 and 200 at 8 pm) resulted in a clinical pregnancy rate of 23% and an implantation rate per embryo of 7.5% compared to a rate of 45% and 19% respectively for i.m. progesterone. Pouly and collaborators [61] showed that oral progesterone (100 mg in the morning and 200 mg in the evening) determined a clinical pregnancy rate of 25% and an implantation rate of 29.9%, in correlation to a pregnancy rate of 28.8% and implantation rate of 35.3% for progesterone vaginal gel. This difference was not statistically significant.

An explanation of the possible mechanism underling these clinical evidences has been given by some authors [63,64]. As stated before, the rapid metabolism of oral progesterone generates a high concentration of circulating metabolites, including the desoxycorticosterone, estrone, and estradiol. The most well known metabolites, the 5α-and 5β-reduced pregnenolone have a concentration, which is higher than that of progesterone itself. Since the metabolites of progesterone are highly concentrated in comparison with their precursor at the plasmatic level, they may bind progesterone receptors and interfere with the normal action of the hormone. Furthermore, the 5α and 5β reduced pregnenolone are known to have a high affinity to the γ-aminobutyric acid receptors [65]. These receptors are present in the reproductive organs (Perusquia *et al*. 1996) and their activation may have deleterious effects on pregnancy outcome. In conclusion, oral progesterone shows a higher compliance even though one must also consider the inconveniences associated with oral progesterone administration primarily in those indications where the therapeutical effect of progesterone must be prolonged [67].

Vaginal Progesterone

The vaginal route of progesterone administration offers many advantages such as lack of local pain, avoidance of first-pass hepatic metabolism, rapid absorption, localization of the bioavailability at the endometrial level [68,69]. This route of progesterone administration does not allow to obtain high plasmatic levels of the hormone, which shows a preferential distribution at uterine level [70,71]. Currently progesterone has been formulated in bioadhesive gel preparations. These preparations show a more complete compliance when compared with cream formulations and suppositories that are known to cause uncomfortable vaginal discharges and subsequently give no regular absorption assurance of the active component [72,73].

The comparison between i.m. and vaginal progesterone has led to controversial outcomes concerning the superiority of one or the other in inducing secretory endometrial transformation [74]. The vaginal administration of progesterone determines high concentration of the hormone at the uterine level. In this condition the first uterine passage may appear detrimental but this may only be true in certain indications such as HRT [75,76]. It is well known that in hormone replacement therapy, once the estrogenic stimulation has occurred, the therapeutical target of progestogens administration is to determine a secretive transformation of the endometrium, since we need to avoid the occurrence of the adverse effects of estrogen. In other indications, as for example in luteal phase support following assisted reproduction the vaginal administration of progesterone has determined a lower pregnancy rate when compared to intramuscular progesterone [77,78]. It has been suggested that in assisted reproduction the secretive transformation of the endometrium should be synchronous in all its tissutal components, and probably if progesterone is administered vaginally this does not happen [79].

Moreover, considering that the implantation of the embryo occurs only with a proper balancing of permitting and blocking factors, we may easily comprehend the importance of a proper timing of the action of all the hormones involved in the process [80]. In fact, depending on its circulating levels, the single hormone may both induce or inhibit the synthesis of permitting/blocking factors. That means that progesterone may either act favouring implantation working as a permissive agent in a certain range of concentrations or as a blocking agent when concentrations are lower or higher in comparison to a cut-off value [81-84]. This consideration is also consistent with the fact that the first contraceptive used in therapy was a high-dosage progesterone preparation. However, it is important to mention that some studies have not discovered statistically significant differences in terms of pregnancy rates in patients undergoing IVF where luteal phase support was given either i.m. or vaginal progesterone [85-87].

Intramuscular Progesterone

The intramuscular route of administration is the most frequently used method of progesterone administration. As regards the pharmacokinetics of progesterone delivered by this route, the definition “intramuscular route of administration” should be substituted with “intergluteal route of administration”. In fact it has been proven that when administered by intergluteal route progesterone half-life seems to be significantly higher in comparison to its half-life

when administered on the superior part of the arm [53]. This may be due to the diverse concentration of adipose cells between the arm and gluteus, given that progesterone displays a high affinity for adipose cells: in fact the hormone is stored in adipose cells, and is then released when plasmatic levels decrease. This effect may resemble a *depòt* effect of progesterone and allows us to perform a daily singular administration even though progesterone half-life is extremely low (5-20 minutes) [88].

The only true discomfort associated with this route of administration is that intramuscularly administered progesterone causes pain at the site of injection, occasionally the formation of a bruise and in rare cases of sterile abscesses [89]. Aside from these minor inconveniences i.m. administration is the only route which guarantees adequate and verifiable plasmatic levels of the active component. In fact, it is quite clear that in assisted reproduction, abortion threatening therapy and in the risk of preterm labor the patients sustain the pharmacological therapy even if it is long and uncomfortable because of their high motivation [90]. Today, a new formulation of progesterone in oil for i.m. administration (100 mg progesterone/1 ml) has dramatically reduced the occurrence of pain at the site of injection. However, this route of administration should not be the preferable one in the indications of menopause where the vaginal route of administration seems to be equally effective and more tolerated by the patient. Here we discuss the literature concerning the i.m. administration of progesterone in threatened miscarriage, recurrent miscarriage and preterm labour.

Threatened Miscarriage

Spontaneous abortion accounts for a great variety of possible causes, which makes difficult to operate a correct prevention and/or therapy. Moreover, it is not uncommon that a threatened miscarriage might settle spontaneously as a consequence of bed rest and/or no treatment. In addition, it is important to stress that vaginal bleeding in early pregnancy is not necessarily synonymous of threatened miscarriage. Consequently, the results of a clinical study on miscarriage threatening can be completely altered by varying the inclusion or exclusion criteria for any given protocol.

Among the different therapeutical options available in the management of threatened miscarriage, one possible way is to try to decrease or to stop uterine contraction. Progesterone has been demonstrated to have a tocolytic action on the myometrium during the pregnancy [1,91,92] with a concentration dependent action [92]. It has been calculated that the daily administration of 100 mg of progesterone intramuscularly results in 0.6 γ/g of hormone for gram of endometrial and myometrial tissue. Progesterone exerts its tocolytic action in early pregnancy at a high-dosage and, according to patient weight, the optimal dose should be between 100–200 mg/day [93]. This dosage has also been proven to have an effective result in the maintenance of uterine quiescence and during cervical cerclage in the first trimester of pregnancy and/or after abdominal surgery, as appendicectomy.

Recurrent Miscarriage

The definition of recurrent miscarriage is the occurrence of three consecutive pregnancy losses. A considerable number of studies have been carried out in order to investigate on the possible causes underlying this disease, but it is not possible to find a recognisable cause in up to half of cases [94]. Among the most frequent causes are luteal phase deficiency and immunotolerance derangements [95,96]. Progesterone stimulates the production of PIBF (progesterone induced blocking factor) which acts against NK cells. The action of NK cells is crucial to implantation and mother/foetus interaction in early pregnancy [97]. Intramuscular and vaginal progesterone, from 100 to 400 mg/day, has been administered and found effective in comparison with placebo in few randomised trials [98-101] (Table **1**).

Table 1. Efficacy of Progesterone in Support of Recurrent Miscarriages: Meta-Analysis of Randomized Clinical Trials

Randomized Clinical Trials	Odds ratio (95% CI)
Tognoni *et al*. 1980	1.29 (0.87–1.51)
Gerhard *et al*. 1997	0.56 (0.13–2.49)
Reijinders *et al*. 1988	1.99 (0.20–19.66)
Total	1.28 (0.50–6.49)

Preterm Labour

Progesterone is profoundly involved in the mechanism that regulates human parturition (at term and preterm). An adequate concentration of progesterone in myometrial tissues is able to counteract the stimulatory activity of prostaglandin as well as the action of oxytocin in enhancing the activity of β-agonists [102]. Progesterone decreases the concentration of myometrial oxytocin receptors, that in turn counteracts the effect of estrogens. Similarly this happens to the number and properties of gap junctions. Progesterone also inhibits prostaglandin production by amnion-chorion-decidua and proved 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.

The administration of high-dosage progesterone has been advocated as a possible tocolytic agent even though 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 manifested synergistic effects by decreasing the necessity for high concentrations of β-agonists, known to have potentially dangerous side effects (Tables **2** and **3**).

The application of prophylactic progesterone at high doses was currently 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 revealed that weekly administration of 17-α-hydroxyprogesterone caproate at 300 mg/day intramuscularly, results in a decrease of almost 50% subsequent incidences of preterm birth before 32 and 36 weeks, irrespective of the aetiology [103]. To conclude, progesterone may be needed either to decrease the concentration of potentially harmful tocolytic

Table 2. Clinical Results of the Association of a Beta-Agonists (Ritodrine) and Progesterone for the Treatment of Preterm Labour (Di Renzo *et al*., Unpublished data)

	Ritodrine	Ritodrine + 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 a β-Agonists (Ritodrine) in Combination with Progesterone (Di Renzo *et al*., Unpublished Data)

Maternal side effect	Ritodrine	Ritodrine + progesterone
Maternal tachycardia	97%	52%
Nausea and vomiting	28%	16%
Tremblings	26%	12%
Palpitations	32%	22%
Chest pain	15%	10%
Hyperglycaemia	47%	28%
Hypokalaemia	92%	53%

drugs, or as a preventive agent in a high-risk population of women at risk of preterm birth.

CONCLUSION

The literature concerning progesterone use in gynaecology and obstetrics and in its various routes of administration is abundant. Few articles have been found related to the use of transnasal, sublingual, rectal and transdermic progesterone. These routes of administration of progesterone in the different indications proposed represent only a minor issue, although in some cases the results of the studies seem encouraging (as for transdermic progesterone). On the contrary, much literature has been found concerning the use of i.m., vaginal and oral progesterone, especially in the following indication: luteal phase support, threatened miscarriage, recurrent miscarriage and preterm labour. Although with the discussed limitation, progesterone has proven to be effective. We can say that the route of administration that demonstrate a better efficacy in all the three major pregnancy pathologies (threatened abortion, recurrent miscarriage and prevention of preterm birth) is the intramuscular route, which ensures adequate and verifiable plasmatic levels.

To conclude, the importance of progesterone in reproduction is unquestionable. Notwithstanding this consideration, and the evidences that progesterone plays a key role in most of the physiologic processes, the use of progesterone in clinical practice remains restricted in the prevention and treatment of threatened miscarriage, recurrent miscarriage and preterm birth. Progesterone is also efficacious when the continuation of pregnancy is limited by immunological factors, luteinic neuroendocrine deficiencies and myometrial

Table 4. Use of Prophylactic Progesterone in High-Risk Patients for Preterm Labour

	Placebo	Progesterone	Relative risk	Confidence interval	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

hypercontractility. This justifies the reduction in the incidence of preterm birth in pregnant women using high-dosage prophylactic progesterone.

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