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Different routes of progesterone administration and polycystic ovary syndrome: A review of the literature

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Abstract
Polycystic ovary syndrome (PCOS) is a common endocrine disorder in woman of reproductive age. Although extensive studies have been performed in past decades to investigate the pathobiological mechanisms underlying the unset of this disease, its etiology remains unknown. Progesterone is a hormone of paramount importance in ovulation, implantation and luteal phase support. Low levels of progesterone have been found in the early luteal phase in PCOS patients. Granulosa cells from polycystic ovaries show an altered progesterone production. Moreover, the lack of cyclical exposure to progesterone may have a role in the development of the gonadotropin and androgen abnormalities found in PCOS patients. Ovulation failure and progesterone deficiency may facilitate the hypothalamic–pituitary abnormalities causing the associated disordered luteinizing hormone secretion in PCOS. Progesterone may be administered to PCOS patients in the following cases: to induce withdrawal bleeding, to suppress secretion of luteinizing hormone, in ovulation induction in clomiphene citrate-resistant patients and in luteal phase support in assisted reproduction. We discuss the pharmacologic characteristics of the different routes of progesterone administration with reference to these diverse indications, the therapeutic objectives and patient compliance.

Keywords: *Polycystic ovary syndrome, progesterone pharmacology, luteal phase support*

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age [1–3]. Although extensive studies have been performed in past decades to investigate the pathobiological mechanisms underlying the unset of this disease, its etiology remains unknown [4].

Progesterone plays an important role in ovulation [5,6], in embryo implantation and in luteal phase support [7–10]. Increasing evidence also indicates that human parturition is initiated by decreased myometrial responsiveness to progesterone, i.e., functional progesterone withdrawal [11–13]. Moreover, we know that the incidence of anovulation and miscarriage in PCOS patients is high [14]. Low levels of progesterone have been found in the early luteal phase in PCOS patients [15,16]. Granulosa cells from polycystic ovaries demonstrate an altered ability to synthesize progesterone both *in vivo* and *in vitro* [6].

The lack of cyclical exposure to progesterone has been suggested to have a role in the development of the gonadotropin/androgen synthesis alterations found in PCOS patients [5]. Ovulation failure and progesterone deficiency may facilitate the development of the hypothalamic–pituitary abnormalities that determine the altered luteinizing hormone (LH) secretion which is characteristic of PCOS [5]. Moreover, adults with PCOS require higher progesterone concentrations to inhibit the gonadotropin-releasing hormone (GnRH) (LH) pulse frequency compared with normal women. This contributes to establishment of the persistently rapid GnRH pulses and elevated LH levels found in PCOS [17].

All these findings may explain the presence of anovulation, the delay in conception and the high

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prevalence of miscarriage that occur in PCOS patients [18]. Moreover, they also reveal the reason why PCOS patients undergoing assisted reproductive techniques represent a great challenge for the fertility specialist [14]. Considering everything mentioned above, in these patients progesterone supplementation in *in vitro* fertilization (IVF) cycles is highly recommended for achieving a successful pregnancy [19].

An impaired adrenal function is a common characteristic of patients with PCOS [20]. Consequently, basal androgen and 17α-hydroxy-progesterone (17-OHP) levels are routinely measured for the hormonal evaluation of suspected PCOS women [21,22]. Androgen levels are generally determined to establish the presence of hyperandrogenemia whereas basal 17-OHP levels are determined to screen for 21-hydroxylase-deficient non-classic adrenal hyperplasia [23]. Generally, to maintain sampling uniformity and avoid increases in 17-OHP levels due to corpus luteum function, these levels are obtained during the follicular phase. However, since most hyperandrogenic patients are oligomenorrheic, it is frequently necessary to administer a progestogen to induce the withdrawal bleeding and properly time the blood sampling [22]. Progestogens such as medroxyprogesterone acetate (MPA) are commonly used to induce withdrawal bleeding in PCOS patients [5]. Recent studies have shown that the administration of progesterone to women with PCOS results in a temporary, although clinically relevant, suppression of circulating androgen levels, which is significantly higher than the one achieved by MPA [22,24]. These observations may favor the use of progesterone to induce withdrawal bleeding in these patients.

Undoubtedly, the treatment of anovulatory PCOS patients who are resistant to clomiphene citrate (CC) is challenging for the fertility specialist. The administration of progesterone before CC therapy has been effective in inducing the responsiveness to CC [25,26] due to the progesterone-related suppression of follicle-stimulating hormone (FSH) and LH secretion.

In summary, in clinical practice we may administer progesterone to PCOS patients in the following cases:

(1) To induce withdrawal bleeding;
(2) To suppress LH secretion in the normalization of the menstrual cycle;
(3) In ovulation induction in CC-resistant patients;
(4) To support the luteal phase after assisted reproductive techniques.

In the present review we discuss the pharmacologic characteristics of the different routes of administration with reference to these diverse indications, the therapeutic objectives and patient compliance.

Different routes of administration of progesterone and its pharmaceutical form

Once the therapeutic need for progesterone has been established, the question is which route of administration should be preferred [27,28]. In general, the route of administration of a drug is chosen on the basis of appropriate anatomic, physiopathologic and pharmacotherapeutic considerations [28,29] rather than practical aspects or even patient compliance. However, it is important to mention that from a pharmacological point of view the main factors that determine the success of absorption of a drug from the administration site are three:

(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 at the tissue level.

As regards therapy with progesterone, all possible administration routes have been used with distinct results.

Transdermal route of administration

The transdermal route of administration would be easy to use because it offers good compliance from the patient. However, it does not permit the achievement of adequate plasma levels of progesterone. In fact, progesterone is a lipophilic compound and is not easily absorbed by the skin [30]. Considering that the daily production of progesterone is on average 25 mg, using the transdermal route of administration about half of the body should be utilized as absorbing surface [31]. The unsuitability of the transdermal administration of progesterone makes difficult to conceive any viable therapeutic application for progesterone administered by this route.

Rectal route of administration

The rectum presents a complex hematic and lymphatic vascularization. The rectal mucosa is not considered an important site for drug administration due to the great variability of absorption [32]. However, emphasis should be placed on the fact that as many active components are absorbed by the rectal mucosa as by other lipoproteic membranes [33] and, indeed, non-ionic and lipophylic compounds are absorbed easily by the rectal mucosa [34]. Some authors emphasize that drugs which are easily metabolized by the liver may be more effective when administered by the endorectal route [29,35]. When an active component is absorbed in the lower portion of the rectum, via the inferior hemorrhoidal veins it reaches the general circulation directly, bypassing the hepatic first-pass elimination. On the contrary, if the compounds are absorbed by the

superior rectal ampulla, they will reach the portal circulation via the superior hemorrhoidal vein [28,35].

This route of progesterone administration, which still does not have sufficient bibliographic support, is used in some Anglo-Saxon countries for hormone replacement therapy (HRT) in combination with estrogen administration. The plasma peak of progesterone is reached 8 h after administration and is followed by a gradual decline of the plasma levels. As mentioned above, 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 [36]. This variability in absorption makes difficult to conceive the practical utility of progesterone administration by this route to PCOS patients in any of the previously mentioned therapeutic targets.

Sublingual route of administration

Few studies have been performed on administration of progesterone by the sublingual route [37–39]. In 1996 Stovall and collaborators [37] used this route of progesterone administration for luteal phase support in patients undergoing embryo transfer. The authors demonstrated that, after the administration of 50 or 100 mg of progesterone dissolved in 1 ml of sublingual suspension, the plasma peaks were reached in 30–60 min and levels were on average 17.61 ± 3.78 ng/ml when 100 mg progesterone was administered. However, the maintenance of adequate plasma concentrations through the day required the administration to be repeated two or three times. Preliminary data of the Iowa Assisted Reproduction Program showed that 400 mg of progesterone has to be administered sublingually every 8 h to obtain plasma levels similar to those achieved with intramuscular administration of 100 mg progesterone/day [40]. Further studies are necessary in order to evaluate the effectiveness of progesterone administration by this route, and hence its potential role in the therapy of PCOS patients.

Transnasal route of administration

Nasal mucosa represents a potential site for progesterone administration due to its high vascularization and the presence of microvilli that expand the absorbing area considerably [41,42]. Such a route of administration was proposed by Steege and co-workers in 1986, and in 1993 Cicinelli and associates evaluated the possibility of progesterone administration through nasal spray [43–46]. The results of this study were very interesting, although the plasma levels achieved did not permit therapeutic effectiveness to be reached in clinical obstetrics and hence in PCOS. This route of administration could be proposed for HRT in menopause [47].

Intrauterine route of administration

The intrauterine route of administration consists of the application of an intrauterine device and is of particular interest in contraception and pre-menopause [48]. Clearly, it cannot be proposed in obstetrics because it would act as a contraceptive [49]. Like for the transnasal route of administration, in this case we also do not reach adequate plasma levels of hormone to propose this route of progesterone administration in any of the therapeutic targets in PCOS mentioned above.

Oral route of administration

The oral route of progesterone administration offers high compliance for the patient even though it presents evident disadvantages. First of all, there is a great variability of absorption depending on individual factors and gastric filling [50,51]. Moreover, oral progesterone shows poor bioavailability [52] and a rapid clearance rate [53].

Progesterone administered by the oral route is first absorbed at the intestinal level and then reaches the liver, passing through the portal vein where it is rapidly converted into metabolites. This enterohepatic passage determines important side-effects such as dizziness, sleepiness, nausea, etc. [7] caused by the formation of these metabolites. In addition, due to the rapid metabolism, plasma levels of oral progesterone tend to be relatively low. Consequently, to reach plasmatic levels that are adequate for an effective therapeutic action, it is necessary to administer high and repeated dosages of progesterone during the day [54,55]. Unfortunately, this makes plasma levels of progesterone metabolites rise further. Therefore, considering the previously mentioned issues, the development of a progesterone-containing drug that could pass throughout the gastric barrier and release the active component at the intestinal level may be advantageous. Consecutive dosages could be reduced in number and also side-effects will occur less frequently.

In recent years an oral micronized preparation of progesterone has become available on the market. This formulation leads to a higher absorption of the active component [52,56] in comparison with the classical oral formulation. The production of micronized progesterone requires transformation of the chemical compound into very fine powder that in turn has to be suspended in an oil vector, a process that may considerably increase its bioavailability [57]. Notwithstanding the process of micronization, the intestinal absorption of progesterone is still limited. Moreover, considerable inter-subject variability in the extent of progesterone absorbed after administration of oral micronized progesterone is still present [50,51]. The absorption of oral micronized progesterone is doubled in the presence of food. However, the bioavailability of oral micronized

progesterone is approximately 10% compared with intramuscular progesterone [52].

Oral micronized progesterone has been administered in IVF for luteal phase support. Studies demonstrated that oral progesterone is associated with a significantly lower implantation rate per embryo compared with intramuscular progesterone in luteal phase support in IVF cycles [58,59]. This difference was observed despite the fact that circulating levels of progesterone were similar in both groups. Buvat and colleagues [60] demonstrated that use of oral micronized progesterone in oil (100 mg at 08.00, 100 mg at 12.00 and 200 mg at 20.00 hours) resulted in a clinical pregnancy rate of 23% and an implantation rate per embryo of 7.5%, compared with 45% and 19%, respectively, for intramuscular progesterone. All these differences were statistically significant. However, Pouly and collaborators [59] reported that oral progesterone (100 mg in the morning and 200 mg in the evening) resulted in a clinical pregnancy rate of 25% and an implantation rate of 29.9%, compared with 28.8% and 35.3%, respectively, for progesterone vaginal gel. This difference was not statistically significant.

We know that the rapid metabolism of oral progesterone leads to a high concentration of circulating metabolites, including deoxycorticosterone, estrone and estradiol. The most common metabolites, the 5α- and 5β-reduced pregnanolone, are present in concentrations higher than that of progesterone itself [61,62]. The metabolites of progesterone, being highly concentrated, may bind progesterone receptors and interfere with the normal action of the hormone. Moreover, the 5α- and 5β-reduced pregnanolone are known to have a high affinity for γ-aminobutyric acid receptors [63]. These receptors are present in the reproductive organs [64] and their activation may adversely effect the outcome of pregnancy.

The clearance of orally administered progesterone has been studied by Whitehead and co-workers [65] in five postmenopausal women. Progesterone 100 mg/day was administered orally for five consecutive days. Progesterone represents an important metabolic step in the biosynthesis of many steroids, including some glucocorticoids and mineralocorticoids. The transformation of exogenous progesterone into other hormones with diverse biological activity represents a limit in clinical practice. Circulating progesterone may be converted into deoxycorticosterone at peripheral tissue level; the extra-adrenal synthesis of this potent mineralocorticoid from endogenous and exogenous progesterone has been well documented [66–68].

Progesterone is widely metabolized at the intestinal and hepatic level by the reduction of the C-3 and C-20 carbonyl groups; by reduction of the C-4 to C-5 double bond; by hydroxylation at C-16 to C-21; and by conjugation with glucuronic and sulfuric acids [69]. Progesterone may compete with mineralocorticoids at the receptor level, thus acting as a mineralocorticoid antagonist [70–72]. Unfortunately, a conspicuous amount of progesterone is converted to deoxycorticosterone [68].

During the menstrual cycle in women of reproductive age, progesterone and deoxycorticosterone levels rise concomitantly, reaching a maximum concentration during the luteal phase [66]. In women during the follicular phase and in men, circulating deoxycorticosterone is produced by the adrenal cortex. On the other hand, during the luteal phase more than 75% of the circulating deoxycorticosterone comes from the peripheral conversion of progesterone [66,67]. The exogenous administration of progesterone is followed by a rapid increase of plasma deoxycorticosterone levels, and the route of progesterone administration may influence the progesterone/deoxycorticosterone ratio. The effects of mineralocorticoids and of deoxycorticosterone are partly antagonized by the antimineralocorticoid effects of progesterone itself. One may hypothesize that some clinical manifestations, i.e., premenstrual syndrome, pregnancy-related edema as well as hypertensive disorders in pregnancy, could be linked to the alterations of the progesterone/deoxycorticosterone ratio.

In conclusion, the oral administration of progesterone offers high compliance even though the associated inconveniences should be taken into consideration, especially in those indications where the administration of this hormone has to be protracted [73]. Conversely, where we need a short therapy, oral progesterone could be preferred to intramuscular administration. For example, this route of progesterone administration could be indicated to induce bleeding in PCOS oligomenorrheic patients, where progesterone is more effective than MPA in suppressing circulating androgen levels [22,24].

Vaginal route of administration

The vaginal route of progesterone administration provides many advantages such as lack of local pain, avoidance of first-pass hepatic metabolism and rapid absorption. However, this route of administration results in localization of the bioavailability of the active component at endometrial level [74–77]; consequently, this route of progesterone administration does not permit high plasma levels of the hormone to be reached.

Recently progesterone has been formulated in bioadhesive gel preparations. These preparations elicit better compliance compared with cream formulations and suppositories, which are known to cause uncomfortable vaginal discharges and consequently an irregular absorption of the active component [78]. Studies comparing intramuscular and vaginal progesterone in inducing a secretory transformation of the endometrium have led to

controversial results regarding the superiority of one or the other [79].

As stated above, vaginal administration of progesterone results in high concentration of the hormone at the uterine level (first uterine passage). This may represent an advantage for certain indications such as HRT [80,81]. After the estrogenic stimulation, in HRT the aim is to provoke the secretive transformation of the endometrium to avoid the adverse effects of estrogen at endometrial level. This effect may not be adequate/advisable in other therapeutic indications. For example, in luteal phase support after assisted reproduction, the vaginal administration of progesterone results in a lower pregnancy rate in comparison to intramuscular progesterone [82,83]. In fact, in assisted reproduction the secretive transformation of the endometrium has to be synchronous in all its tissue components. This does not occur if progesterone is administered vaginally [84].

The rational behind these clinical findings may be easily understood if one considers that implantation of the conceptus may only occur with a balancing of permitting and blocking factors [85]. These factors are hormone-dependent in the sense that circulating levels of the single hormone may both induce and inhibit the synthesis of these factors, depending on the concentration of the hormone itself. That is to say, progesterone may act either towards implantation as a permissive factor in a certain range of concentration or as a blocking factor when its concentrations are lower or higher than a cut-off value [86,87]. This is evident if we remember that the first contraceptive used in therapy was a high-dosage progesterone preparation. However, some studies have not found statistically significant differences in terms of pregnancy rates in patients undergoing IVF where luteal phase support was given by either intramuscular or vaginal progesterone [88–90].

Intramuscular route of administration

The intramuscular route of progesterone administration is the one most commonly used for this hormone in clinical practice. With reference to the pharmacokinetics of intramuscular progesterone, the definition 'intramuscular route of administration' should be substituted with 'intergluteal route of administration'. It has been shown that when progesterone is administered by an injection into the gluteus, its half-life is significantly longer than when the hormone is injected into the superior part of the arm [52]. This difference may be determined by the different concentrations of adipose cells between the arm and gluteus: in fact, progesterone shows a high affinity for adipose cells. Consequently, after administration of the hormone into the gluteus, progesterone is stored in adipose cells and released only when the plasma levels decrease. This effect may be defined as a *depot* effect of progesterone, which permits a singular daily administration of the hormone even though progesterone's half-life in the blood is extremely short (5–20 min) [91].

Unfortunately, the intramuscular administration of progesterone causes pain at the site of injection, sometimes the formation of a bruise and, in rare cases, sterile abscess [92]. On the other hand, intramuscular administration is the only route that guarantees adequate and verifiable plasma levels of the active component. It is clear that in assisted reproduction, and in therapy to reduce the threat of abortion and the risk of preterm labor, patients tolerate the discomfort related with the therapy because of their high level of motivation [93]. Conversely, this route of administration does not seem to be recommended in menopause, where the vaginal route seems to be equally effective and more tolerated by the patient.

In conclusion, for all the reason mentioned above concerning the intramuscular route of progesterone administration, this should be preferred in the treatment of PCOS patients in the case of CC resistance in ovulation induction and, obviously, for luteal phase support after assisted reproduction.

Studies of progesterone use in polycystic ovary syndrome

As mentioned in the Introduction, it has been suggested that the lack of cyclical exposure to progesterone may play an important role in the development of gonadotropin and androgen abnormalities in PCOS [5]. Furthermore, progesterone may also be involved in PCOS-associated anovulation and miscarriage [6].

It is known that an increment in LH level is a typical finding in PCOS patients. This unsuitable elevation of LH is suspected to adversely influence follicular development and ovulation. In the study of Buckler and associates [94], progesterone was administered because of its suppressive action on LH secretion (if progesterone is administered continuously in physiological dosages). Ten PCOS patients were treated with vaginal progesterone 100 mg twice a day for 10 days. Mean serum progesterone levels reached 16 ng/ml 4 days after the treatment and remained in the mid-luteal phase range thereafter. The mean serum LH concentrations decreased significantly ($p \leqslant 0.01$) after 8 days of treatment and continued to fall progressively until the end of progesterone administration. In another study of Pastor and collaborators [95], LH levels were normalized when progesterone vaginal suppository and transdermal estradiol were administered, reaching plasma progesterone concentrations of 13–15 ng/ml. These results are in contrast to those of other studies in which the administration of vaginal progesterone did not permit the achievement of high and stable plasma levels of progesterone [79,81,96]. In conclusion, although further studies should be

Table I. Summary of the possible therapeutic approaches in the treatment of patients with polycystic ovary syndrome (PCOS) in relation to the diverse indications in which progesterone could be used.

Indications in PCOS	Route of progesterone administration	Dosage
Induction of withdrawal bleeding	Oral	100 mg in the morning and 200 mg before bedtime for 7 days
Suppression of luteinizing hormone secretion	Vaginal	100 mg twice a day for 10 days
Ovulation induction in clomiphene citrate-resistant patients	Intramuscular	50 mg/day for 5 days
Luteal phase support after assisted reproductive techniques	Intramuscular	50 mg/day from the beginning to the 12th week of gestation

undertaken before assessing a definitive therapeutic role of exogenous administration of progesterone in PCOS, the possibility to normalize LH levels in PCOS patients with progesterone administration has been found effective.

Progesterone plays an important role in oocyte fertilization and embryo implantation. Therefore, when performing assisted reproduction in PCOS patients, progesterone supplementation in these patients is highly recommended in order to achieve a successful pregnancy [18,19,97]. Since the most reliable and stable plasma levels are achieved only with the intramuscular route of administration, treatment with intramuscular progesterone at a dosage of 50 mg/day from the beginning to the 12th week of gestation is suggested.

Progesterone can also be used in ovulation induction in PCOS patients who have been found to be CC-resistant. The pretreatment with progesterone results in suppression of the secretion of FSH and LH, which in turn restores the responsiveness to the estrogenic treatment [25,26]. Ten PCOS women previously found to be CC-resistant were administered 50 mg progesterone intramuscularly for 5 days. After the treatment, in seven of these women LH and FSH levels fell. Consequently, the responsiveness to CC was restored and three of the seven women conceived in the first treatment cycle. The women in whom LH levels were not suppressed remained unresponsive to CC.

Regarding the induction of bleeding in PCOS oligomenorrheic patients, we have reported the results of some studies showing that the use of progesterone to induce withdrawal bleeding results in a temporary although clinically relevant suppression in circulating androgen levels [22,24] which is significantly higher than the one provoked by MPA. These observations may favor the use of progesterone to induce withdrawal bleeding. For this indication the best route of administration may be the oral one (100 mg in the morning and 200 mg before bedtime for 7 days).

Table I summarizes the therapeutic approaches in PCOS patients.

Conclusions

The production of progesterone in PCOS patients is often inadequate. This impairment has been correlated not only with occurrence of anovulatory cycles, but also to the reduced ability of granulosa cells to synthesize progesterone [6].

The lack of cyclical exposure to progesterone has been suggested to have a role in the development of alterations in the synthesis of gonadotropins and androgens found in PCOS [5]. The deficiency in progesterone production and ovulation failure may facilitate the development of the hypothalamic–pituitary alterations that in turn provokes the alteration in LH secretion which is typical of PCOS [5]. PCOS patients require higher progesterone concentrations to inhibit the GnRH (LH) pulse frequency in comparison to normal women.

In conclusion, the use of progesterone in PCOS patients may have different therapeutic objectives. As shown in the present review, the different routes of administration as well as its pharmaceutical form strongly modify the bioavailability and metabolism of progesterone. Hence its therapeutic effects may show a significant difference and this in consequence may affect the possibility of the occurrence of side-effects.

We may conclude by saying that the choice of the modality of progesterone administration has to work with the therapeutic objectives. Consequently, this choice should be guided by the patient's compliance only if the therapeutic options in terms of administration route and pharmaceutical form lead to the same desired efficacy of treatment.

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