Progesterone Function in Human Endometrium: Clinical Perspectives

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ABSTRACT

Progesterone is essential for endometrial receptivity and successful establishment of pregnancy. Either an insufficient progesterone concentration or an insufficient response to progesterone, therefore can lead to infertility and pregnancy loss. Assessment of the role that either progesterone insufficiency or inadequate progesterone response plays in human reproductive failure has been difficult to assess because serum progesterone concentrations fluctuate markedly, limiting the ability to characterize sufficiency of progesterone, and there are no highly reliable markers of endometrial function available. Recent evidence demonstrates exquisite sensitivity of normal endometrium to very low levels of progesterone stimulation, suggesting that progesterone insufficiency should not be a common cause of reproductive failure. Further evidence suggests that women with endometriosis, and possibly polycystic ovarian syndrome, have an altered progesterone response, which may explain some of the clinical features of these disorders and supports the hypothesis that progesterone resistance underlies some cases of human reproductive failure.

KEYWORDS: Luteal phase defect, progesterone resistance, endometrium, embryo implantation, endometriosis

Progesterone (P) is a sex steroid essential for pregnancy and lactation produced almost entirely by the ovarian corpus luteum (CL) and the placenta. Normal endometrial function requires both estrogen (E), which mediates cell growth and induction of progesterone receptors (PR), and P, which counteracts E stimulation and downregulates the receptors for E and P. The normal balance achieved by sequential actions of E and P is essential to the normal cyclic functions of human endometrium, and disruption of this balance is a significant factor in the pathogenesis and/or pathophysiology of many clinical problems, including endometriosis, infertility, abnormal bleeding, pregnancy loss, and cancer.

The mechanisms governing P action on endometrium are complex, involving at least two receptor subtypes (PR-A and PR-B), with distinct expression patterns and functional profiles as well as other putative P receptors, whose identity and function remain an active area of research.[1] The effects of PR-A and PR-B are further modulated by differential expression and activation of coregulators such as SRC1–3. Furthermore, many of P's important effects on endometrium are indirect, via paracrine and autocrine factors.

Although mechanistically complex, P is essential for successful embryo implantation and pregnancy maintenance. Therefore, levels of circulating P below some undefined threshold or resistance of endometrium to

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otherwise adequate P will result in infertility or pregnancy loss. This concept of insufficiency of P action on endometrium comprises the pathophysiological concept of luteal phase deficiency. However, whether sufficiently low P or sufficiently resistant endometrium is encountered clinically remains to be demonstrated definitively. In this article, we focus on the role of sex steroids in endometrial function in women and review the evidence for P insufficiency versus P resistance, using clinical examples that illustrate the importance of appropriate P action.

HISTORY

The importance of sex steroids was first recorded by Aristotle in 350 BCE when he reported the dramatic changes in the cockerel following removal of the gonads. Berthold[2] transplanted testes into a capon and demonstrated comb growth. In the 1920s, Allen and Doisy demonstrated that follicular fluid from porcine ovaries was capable of inducing estrus in the female.[3] Hisaw and colleagues showed how these extracts also inhibited ovulation[4] and induced deciduomata formation.[5] Allen and Corner performed classic studies on the requirement for CL extract on secretory transformation and pregnancy maintenance.[6] These early studies identified what would later be known as estrogen and progesterone, and they illustrated their complex counterregulatory functions in reproduction.

The subsequent discovery of specific receptors for E and P allowed researchers to define tissue sensitivity in molecular terms.[7–10] For the most part, nontarget tissues lacked receptors, and responsive tissues expressed and regulated the levels of these proteins. Recognition of hormone effects in cell types adjacent to those with receptors led to the appreciation of paracrine effects of steroid hormones.[11–14] Further refinement of our understanding of sex hormone effects came with the development of the estrogen receptor (ER) null-mutation "knockout" mouse,[15,16] which ironically was published the same year that a human subject was identified who lacked functional ER-α.[17] Subsequent development of the PR knockout[18] further facilitated our ability to assign specific actions to each steroid hormone.[19,20] The availability of cells derived from each type of mouse provided confirming evidence regarding the paracrine actions of both E[21] and P[22] in the mouse uterus.

Clinical examples of deficiency of sex steroids or their receptors have also been well described. For example, inactivating mutations of the androgen receptor in the XY fetus results in a female appearance.[23,24] Although deficiency of functional receptors for the other sex steroids are exceedingly rare,[17] deficiency of E itself forms the basis for the wide range of disorders seen in rare women with deficient aromatase enzyme activity and all women at menopause. P deficiency states also occur frequently in women with anovulation.[25–28] More subtle defects in P deficiency have long been postulated as a root cause of infertility and pregnancy wastage.[29,30] More recently, deficiencies in P action rather than P amount have been suggested as a cause of infertility and pregnancy loss associated with the diagnosis of endometriosis.[31]

PROGESTERONE AND ENDOMETRIAL PROTEINS

The action of P in the endometrium is predicated on E priming. In response to E, endometrial cells acquire the PRs that increase in number throughout the proliferative phase.[32] P counters the action of E by reducing E receptors and inducing E-metabolizing enzymes. At the same time, P limits its own direct effect on endometrial epithelium but not stroma by greatly limiting expression of PR. These disparate effects on the stroma and epithelium drive the endometrium to a state of receptivity to embryo implantation. In nonconception cycles, further effects of P prepare the endometrium for menstruation and with P withdrawal, orchestrate the induction of a myriad of proteins responsible for digestion and shedding of the spent endometrium.

These changes in endometrial response to P have been recently characterized using advanced molecular microarray techniques.[33,34] Such advancements could not have occurred, however, without the many sentinel studies on endometrial proteins that preceded them. Two of the first major endometrial proteins discovered were insulinlike growth factor-binding protein 1 (IGFBP-1, also known as placental protein 12) and glycodelin (also known as progesterone-associated endometrial protein or placental protein 14). Glycodelin and IGFBP-1 represent the most abundantly expressed proteins in response to P, and both were initially but erroneously thought to originate from the placenta.[35–43] As the name implies, IGFBP-1 binds the insulinlike growth factors, IGF-I and IGF-2, and can alter the growth factors' interactions with cognate receptors IGFR1 and IGFR2.[44–46] IGFR1 and 2 are present in the epithelial compartment with maximal expression during the late secretory phase extending into pregnancy.[47–49] IGFBP-1 is a major secretory product of the decidua in response to P,[50–52] increased by epidermal growth factor (EGF) but inhibited by insulin. IGFBP-1 inhibits mitosis in endometrial stromal cells,[53] and it may have a role in embryo attachment as well as invasion.[54]

Glycodelin is maximally produced during the midsecretory phase in response to P. Aside from being a marker of P action,[55–57] glycodelin likely plays a role in preventing late fertilization of oocytes,[58] contributes to the immune response in pregnancy,[59–61] and plays a role in epithelial differentiation.[60] Glycodelin is associated

with pinopode structures on receptive endometrium, and its expression is associated with downregulation of the PR-B isoform.[61] Although the physiological roles for glycodelin and an understanding of its relative importance remains incomplete, the usefulness of this molecule to scientists lies in its close association with the actions of P, providing a noninvasive measure of P activity during the menstrual cycle.

Complement proteins represent a major group of proteins that appear in the endometrium at the time of peak P. We and others have demonstrated that expression of complement C3 subunit, factor B, and decay accelerating factor are all associated with the midsecretory phase endometrium, suggesting an important role for the alternative pathway during this cycle phase.[62–65] Integrins, osteopontin, and CD44, also expressed during this time in the cycle,[66,67] have been implicated as having a role in limiting complement activation.[68–70] Thus, under physiological conditions, the effects of complement on the embryo are likely muted, but under certain conditions such as endometriosis, increased complement expression has been noted.[71–73] Increased complement activation is associated with fetal wastage in animal models, leading some to speculate that this may be an underlying cause of pregnancy loss.[74–76]

A recent series of reports highlighted the expression of a class of innate immune receptors, the Toll-like receptors (TLRs), in the endometrium.[77–80] Interestingly, one TLR, TLR3, appears to be limited largely to the epithelial layer of endometrium and cycle regulated in its expression with maximal expression during the mid and late secretory phases. The role of TLR3 at this time remains unclear, although it may simply be associated with increased innate immune activity to compensate for the relatively muted adaptive immune response. Interestingly, activation of TLR3 leads to a very robust expression of type I interferons, which are known to be important in embryo implantation of ruminant species, suggesting a potential role for TLR3 in the implantation process.

PROGESTERONE AND UTERINE RECEPTIVITY

P is absolutely essential for pregnancy as demonstrated by the early removal of the CL[81] or by administration of PR antagonists such as RU-486 (mifepristone).[82,83] During the early phases of the secretory phase, when ERs and PRs are plentiful, the endometrium differentiates into a secretory tissue, in response to both E and P.[84] By the midsecretory phase, ER abundance falls in all compartments, PR B isoform is suppressed, and the stroma becomes the focus of P action. This loss of E action may determine which proteins are expressed in the epithelium,[85] and P-induced paracrine factors from the stroma also dictate epithelial gene expression.[86] What is clear from DNA microarray studies is that the receptive endometrium is a specialized structure that is both secretory and differentiated. Cell adhesion molecules (CAMs) are increased at the apical surface and loosened at the lateral attachments. Underlying stroma becomes "epithelialized" in preparation for trophoblast invasion. Specialized changes in the luminal epithelium provide an opportunity for embryo–endometrial interactions. None of these changes occur in the absence of P.

Changes in the extracellular matrix (ECM) have been described throughout the menstrual cycle[87] extending into pregnancy,[88] reflecting the role of CAMs in embryo–endometrial interactions.[89] Integrins are cell-adhesion molecules that serve as receptors for extracellular matrix.[90] Dynamic changes occur in integrin expression during the menstrual cycle and into pregnancy.[91–94] The three amino acid motif arg-gly-asp (RGD) was implicated in implantation by several investigators.[95–97] RGD is present on many ECM ligands in the receptive endometrium, including osteopontin, IGFBP-1, and fibronectin.[98–101] RGD peptides were shown effectively to block implantation or attachment of embryos in vitro, suggesting a critical role of integrins and related ligands to endometrial receptivity.[100–104]

P actively blocks the actions and effectiveness of E in the endometrium.[105] Aside from downregulation of E receptor, P induces 17β-hydroxysteroid dehydrogenase-type 2 (HSD17β2) in endometrium that mediates the conversion of estradiol to the less active estrone.[106] Thus both local E concentration and response are decreased. A loss of E action appears critical to the acquisition of endometrial receptivity, not only in humans, but among most, if not all, placental mammals.

In women with endometriosis[107] or polycystic ovary syndrome (PCOS),[108] increased E receptor abundance during the secretory phase appears to be a primary defect, suggesting the presence of P resistance. In both endometriosis and PCOS,[109,110] deficient levels of HSD17β have also been described. Excessive production of E via aberrant expression of aromatase may contribute to this imbalance noted in certain pathological states.[106] Whatever the mechanism, defects in P action alter the balance between E and P activity and likely influences numerous other steps in the acquisition of endometrial receptivity for embryo implantation.

P interacts with its receptor and other transcription factors including heat shock proteins, immunophilins, and coactivators that facilitate gene expression in target tissues. The immunophilin FKBP52 is a chaperone protein for PR and is critical to implantation in the mouse.[111,112] Intriguing studies from the baboon model suggest that reduced FKBP52 is associated with endometriosis. This defect may explain in part the P resistance associated with this disease.[31]

PROGESTERONE IN THE CLINIC

Although P is essential for pregnancy, the amount of circulating or bioavailable P that is required is unknown. Normal standards of midluteal P have been assigned based on population studies, but the lower limits of P have only recently been explored.[113] In this section we review the many facets of P deficiency and highlight the obstacles to a better understanding of what P deficiency actually implies.

Luteal Phase Defect

Luteal phase defect (LPD) is a disorder thought to be characterized by insufficient P production resulting in inadequate endometrial receptivity leading to infertility and pregnancy wastage. For many years, the histological appearance of the endometrium was assumed to be a sensitive measure of P action and thus endometrial function. The histological changes in the endometrium in response to ovulation were first examined by Rock and Bartlett in 1937.[114] The hypothesis that alterations in endometrial histology would reflect functional capacity and thus fertility was first hypothesized by Georgeanna Seegar Jones in 1949.[115] The criteria that defined the chronological dating of secretory endometrium was published a year later in 1950, in what has become the most cited paper in gynecologic literature.[116] The endometrial biopsy was proposed as the most direct approach for the assessment of P effect. From the standpoint of the embryo, the end result and cumulative effects of P are manifest in an endometrium that is functional and ready to accept the nascent embryo.

Based on the Noyes criteria, endometrial dating had been touted to be good predictive value for chronological dating.[117,118] Unfortunately, the timing of the endometrial biopsy has changed over time; late endometrial biopsies were advocated prior to the availability of urinary ovulation predictor kits, whereas earlier biopsies are now advocated to maintain proximity to the window of implantation.[119] Timing of the biopsy appears to alter the degree of variability in histological dating appearance, and the variability of histological dating has been shown to be so large that accuracy and reliability are not sufficient to justify the use of endometrial dating as a bioassay for P action.[120–123] Thus, despite 60 years of study, the usefulness of endometrial histology for the assessment of infertility remains in doubt.

Because the theory of LPD centers on inadequate P production, it stands to reason that low circulating P concentrations at the midluteal phase might be considered the sine qua non for the diagnosis of LPD. Certainly a myriad of studies have examined the use of serum P in the evaluation of LPD.[124] Using frequent P measurements, researchers have suggested that integrated P levels correlate with the quality (histology) of the secretory endometrium.[125–128] Abraham suggested that three determinations of P >15 ng/dL was sufficient to exclude LPD.[127] Others suggest that single determinations of P4 are sufficient.[128] Levels as low as 3 ng/mL or as high as 10 ng/mL have been proposed. However, P is secreted in pulses and cleared relatively rapidly, resulting in large excursions in serum concentration.[129] Thus, one or even a few measurements of serum P are not likely to be a reliable determinant of endometrial function. Furthermore, most of the evidence has rested on changes in endometrial histology, which, as discussed earlier, lacks sensitivity and specificity as tests of fertility.

If P insufficiency exists, alterations in CL function would likely be a cause.[130] The functional capacity of the CL may depend on the follicle from which it was derived, and poor folliculogenesis could be a result of a poor quality oocyte and/or pituitary problems. Alternatively, delayed implantation due to endometrial dysfunction could lead to a delay in human chorionic gonadotropin signaling to the waiting CL. In this case, a perfectly normal CL may produce inadequate P by virtue of a late rescue from a tardy embryo. Such a mechanism appears quite likely based on population studies involving the timing of implantation.[131] Any systemic disorder that alters ovulatory or endometrial function could potentially alter the quality of the follicular maturation, CL formation, CL rescue, or acquisition of uterine receptivity.

Other endocrine conditions may also impact on reproductive function. Hyperprolactinemia is an example of a systemic disorder linked to LPD. Wenner was the first to suggest the association between hyperprolactinemia and LPD.[132] Subsequently, other authors have reported the finding of a shortened or inadequate luteal phase in hyperprolactinemia.[133–138] Hypothyroidism may likewise alter the hypothalamic-pituitary-ovarian axis and can be associated with elevated prolactin levels,[139] leading to reduced P action and possibly LPD.[140] Elevated androgen levels, such as those seen in PCOS, have been associated with LPD,[141] suggesting a mechanism for the poor reproductive performance noted in this diagnosis.[141] Even recreational running may lead to evidence of P insufficiency.[142]

As can be appreciated from the preceding discussion, problems with investigation of LPD include potential heterogeneity and overlap with other reproductive disorders. Furthermore, normal and abnormal individuals may be intrinsically different, so that a response to a defined amount of P in one woman may be significantly less than the response in someone else. To address the heterogeneity as well as the imprecision of serum P measurements, we recently studied normal fertile controls in an artificial hormonally controlled cycle.[113] These normal individuals maintained normal midsecretory endometrial histology as well as expression

of selected marker genes despite steady-state levels of P of ~4 ng/mL.

Despite the lack of apparent difference between normal and low P in otherwise normal women in our protocol, P supplementation has proven benefit for fertility. During in vitro fertilization (IVF) cycles, P supplementation increases clinical pregnancy rates, especially within cycles using gonadotropin-releasing hormone analogues.[143–145] Therefore, lowered P concentrations in IVF patients likely results in lowered fertility, and P supplementation restores fertility.

Because P levels approaching the lowest of those seen in ovulatory women supports normal endometrial structural and functional maturation in normal individuals, but infertility patients appear to benefit from higher P concentrations, it is possible that it is a difference in P response that determines LPD, rather than the absolute P concentration (Fig. 1).[146] The explanation may be as simple as reduced or altered PR expression or as complex as epigenetic changes in specific genes. In an early study by McRae and Lyttle, steroid receptors for ER and PR were initially found be similar between women with normal cycles and those with LPD.[147] Others report that both ER and PR levels are lower in LPD and that the PR:ER ratio is a reliable indicator of LPD.[148] More recent work in this area is extensively covered elsewhere in this issue of *Seminars in Reproductive Medicine*. Clearly, there remains much to study in this new area of P resistance.

As can be well appreciated from the preceding discussion, LPD, outside of an abnormally short luteal phase, is impossible to diagnose accurately with currently available clinical tools. Evidence suggests that assessment of circulating P is subject to difficulties in measurement. Furthermore, even if those difficulties could be obviated by frequent or integrated serum or urinary measurements, the critical issue of differences in endometrial response to P would be missed. Therefore biomarkers, whose endometrial production is inhibited or increased by P, are the most logical area of development for the diagnosis of LPD.

Biomarkers of Progesterone Action

Many biomarkers of P activity have been proposed over the years. With the availability of specific mono- and polyclonal antibodies, immunohistochemistry was proposed to supplant histological dating.[148–151] The advent of DNA microarray techniques and other advanced molecular techniques have dramatically increased the number of candidate biomarkers of P action.[152–155] Infertility and recurrent pregnancy loss are often attributable to defects in implantation.[131,156,158] Given the role of P on maintenance of pregnancy, and the

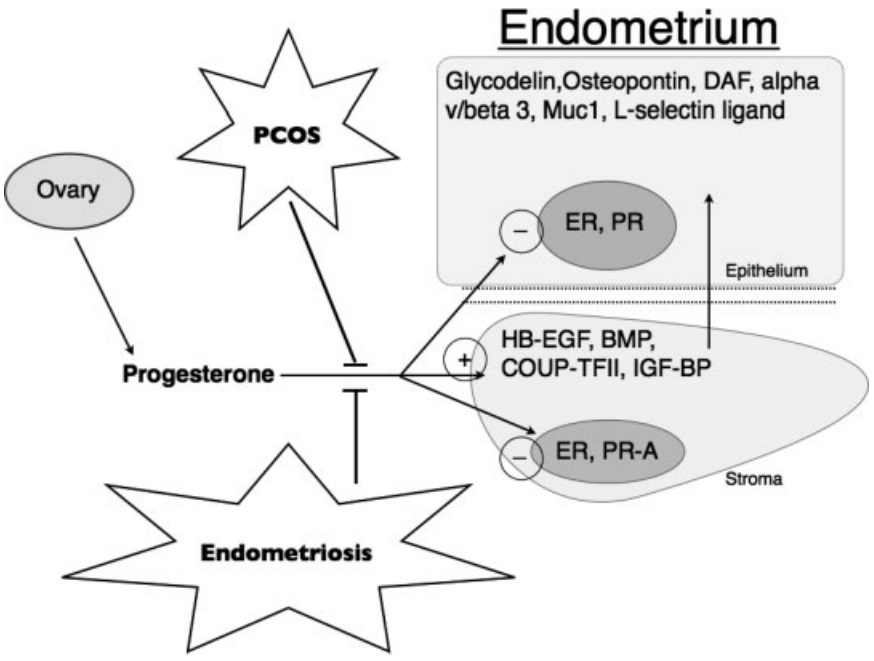

Figure 1 Progesterone (P) actions may be blocked in women with endometriosis or polycystic ovarian syndrome (PCOS). P, derived from the corpus luteum, acts differentially in the stromal versus epithelial cells, resulting in altered expression of several molecules important for embryo implantation. In epithelial cells, P downregulates all estrogen receptor (ER) and progesterone receptor (PR) forms, whereas in stromal cells, ER and PR-A are downregulated while PR-B persists. In women with PCOS or endometriosis, some of the actions of P may be altered, leading to diminished endometrial receptivity to embryo implantation. COUP-TFII, chicken ovalbumin upstream promoter transcription factor II; BMP, bone morphogenetic protein; DAF, decay accelerating factor; HB-EGF, heparin-binding EGF-like growth factor; IGFBP, insulin-like growth factor-binding protein.

importance of synchronous interactions between the endometrium, CL, and embryo, delayed implantation for any reason could contribute to pregnancy wastage.[131,157] It is estimated that 50% of all pregnancy failures during IVF cycles are due to defects in uterine receptivity.[156,159] The use of biomarkers that measure the activity of P in the endometrium has gained favor and provides an alternative to histological dating alone.[160–163]

The first endometrial biomarkers were identified by two-dimensional electrophoresis using a radioactive label.[164,165] Patterns of secreted histones assayed by thin layer chromatography were reported to be potential markers of P's effects on the endometrium.[166,167] With the advent of specific monoclonal and polyclonal antibodies, and immunohistochemical methods as well as microarray technology, there are now a greatly expanded number of biomarkers to investigate.[34,163,168–174]

Integrins and Cell Adhesion Molecules

Dynamic changes in integrin expression during the menstrual cycle provide the opportunity to examine the functional quality of the endometrium during the time of peak P secretion.[91,92] Integrins are arguably the best characterized markers of P effect on the endometrium. In 1992 we described both constitutive and cycle-dependent integrin changes that framed the window of implantation.[91,92] Three integrins (α1β1, α4β1, and αvβ3) are coexpressed in receptive endometrium during the time of maximal endometrial receptivity. The αvβ3 integrin appears at the opening of the window of implantation around cycle day 20 or 21 and is present on the apical pole of the luminal epithelium corresponding to the site of pinopode expression. This integrin is regulated by EGF and EGF-related molecules, and by the transcription factor Hoxa10.[65,175,176] Of note, the appearance of this integrin corresponds closely to the downregulation of ERα in receptive endometrium. In cycles where P fails effectively to downregulate ER, this integrin does not appear normally on cycle day 20.[106] Recent data also suggests that αvβ3 integrin associates with osteopontin. This secreted protein also appears around days 19 to 20, is regulated by P, and may bind to the α v/β 3 integrin through its RGD sequence.[177]

Selectins/Cadherins

L-selectin is a member of the selectin family and may be a key molecule involved in the initial attachment of the embryo.[178] The ligand for this selectin, a sialyl glycoprotein, is P regulated and appears on the receptive endometrium at the midluteal phase, and it is recognized by the monoclonal antibody MECA-79. The distribution of the antigen recognized by MECA79 has now been studied in normal cycling women during the menstrual cycle[179] and may be a clinically useful marker of endometrial receptivity and P action.[180]

Another class of cell-adhesion molecules in the endometrium is the cadherins. These are calcium-dependent transmembrane molecules that have been designated as E-, P,- and N-cadherins. On most normal epithelial cells E-cadherin is involved in lateral attachments between cells and regulated by intracellular calcium. The link to P in endometrium is likely through the action of calcitonin, a P-induced protein in both human and rodent endometrium.[181,182] Calcitonin functions to increase intracellular calcium that in turn attenuates E-cadherin expression at the time of peak P and implantation.[183] Another cadherin, cadherin 11, is present in endometrial stroma and also regulated by P. This key marker of decidualization has been proposed as a mediator of endometrial–trophoblast interaction.[184,185]

Growth Factors

P appears to regulate other key pathways through its influence on growth factors or cytokines. The EGF family of growth factors and their receptors play an important role during implantation.[186,187] In the mouse uterus, heparin-binding EGF-like growth factor (HB-EGF) is expressed around the blastocyst during early implantation. HB-EGF has both a soluble and transmembrane forms. As a transmembrane "receptor," HB-EGF could serve as an embryonic receptor through the EGF receptor on the embryonic epithelium.[188] As a soluble factor, HB-EGF significantly improves embryonic development.[188] HB-EGF has been implicated in the regulation of key endometrial receptivity proteins.[67,189] We showed that P regulates the expression of HB-EGF in endometrial stroma and linked its expression to the regulation of the α v/β 3 integrin via HOXA10 using a paracrine mechanism of action.

SUMMARY REMARKS

P action on the endometrium is essential for embryo implantation and pregnancy maintenance. These "progestational" functions of P are achieved by direct and indirect regulation of many molecules known to play important roles in embryo implantation. At some lower threshold of concentration, there will not be sufficient P action on the endometrium, resulting in infertility or pregnancy loss. Recent evidence demonstrates that in young fertile women, the minimum P concentration required for normal endometrial maturation is very low, perhaps lower than that seen in ovulatory women. This finding suggests that low P, as an isolated abnormality, is not likely to be a common cause of infertility or pregnancy loss. Recent data demonstrating altered effects of P on endometrium of women with endometriosis suggests that resistance to some actions of P may more

commonly underlie reproductive disorders. The hypothesis of P resistance as an important pathophysiological process remains an attractive, but unproven hypothesis with currently unclear mechanisms. However, if the hypothesis is proven, it will open a new avenue of approach to clinical therapies for reproductive disorders.

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