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Review

# Progesterone Action in the Myometrium and Decidua in Preterm Birth

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## *Abstract*

**Progesterone is central to many reproductive processes and is critical in regulating the menstrual cycle and maintaining pregnancy. We discuss here similarities in the molecular mechanisms that regulate the process of decidualisation in endometrial stromal cells and uterine quiescence in myometrial smooth muscle cells. We discuss recent evidence that the decidua may be an important mediator of progesterone actions in the onset of labor in mammalian species lacking progesterone withdrawal. These observations have relevance to recent clinical observations of the effect of progesterone administration in the prevention of preterm labor. We suggest that further research is required to understand the role of progesterone in maintaining the decidua in late pregnancy and particular focus should be given to the mechanisms that increase prostaglandin production in the uterus at term.**

*Key words:* **Decidua, myometrium, parturition, preterm labor, progesterone, uterus.**

## Introduction

Progesterone (P4) exerts a broad spectrum of physiological actions in the cardiovascular and respiratory systems, kidney, adipose tissue, bone, testis and the brain (Graham and Clarke, 1997; Gellersen et al., 2009; 2010). The primary target, however, is the female reproductive tract where P4 has facilitatory roles in modulating the contractile waves of the junctional myometrial zone, tubal transport, and cervical secretion. These processes are superseded by indispensible P4 functions in follicular growth, ovulation and luteinization, embryo implantation, decidualization and maintenance of pregnancy during gestation. We summarise here the actions of P4 in the gravid uterus, focusing on common mechanisms that operate in the myometrium and decidua that may be relevant to term and preterm labor.

## Progesterone and decidualisation

During the menstrual cycle, the luminal epithelium and underlying endometrial stroma undergo substantial transformation that renders the uterus receptive to embryo implantation (Dey et al., 2004; Brosens et al., 2009). This transformation is a highly coordinated and sequential response to the postovulatory rise in P4 levels, commencing with arrest of estrogen-dependent epithelial cell proliferation, followed by the secretory transformation of the glands, recruitment of various bone marrow-derived immune cells, and angiogenesis (Brosens et al., 1999; Gellersen and Brosens 2003; Gellersen et al., 2007). The actions of P4 are primarily mediated by differentiating stromal cells (Simon et al., 2009). This process, termed 'decidualization', is characterized by a mesenchymal-epithelial transition that transforms endometrial stromal cells into specialized secretory decidual cells (Dey et al., 2004; Gellersen et al., 2007; Cloke et al., 2008). Once decidualized the endometrium relies on a constant supply of P4 to maintain the integrity of the tissue. In the absence of successful implantation, the corpus luteum involutes and declining P4 levels trigger a switch in the secretory phenotype of the decidualizing stroma. This change in phenotype entails release of pro-inflammatory cytokines, chemokines and matrix metalloproteinases, leading to breakdown of the superficial endometrial layer, focal bleeding and menstrual shedding (Marbaix et al., 1995; Kokorine

et al., 1996; Brosens and Gellersen, 2006; Brosens et al., 2009; Brun et al., 2009; Gaide Chevronnay et al., 2009). In addition to the ability to undergo apoptosis upon P4 withdrawal, decidualized stromal cells display a number of unique properties commensurate with their function to safeguard the early conceptus, including resistance to oxidative stress induced cell death, the ability to regulate local immune responses and to coordinate trophoblast invasion (Labied et al., 2006; Gellersen et al., 2010; Leitao et al., 2010; 2011).

Endometrial responses to P4 are primarily transduced through binding to, and activation of, the nuclear receptors PR-A and -B, members of the superfamily of ligand-activated transcription factors (Misrahi et al., 1987). In addition to the primary genomic response, it is recognised that there are more rapid short-term actions of P4 that are independent of the transcriptional machinery. In contrast to genomic mechanisms the precise non-genomic actions of P4 are not well defined and are reviewed in detail elsewhere (Gellersen et al., 2009).

The nuclear receptors PR-A and PR-B are members of the nuclear steroid receptor family that share structure with the estrogen, androgen, glucocorticoid and mineralocorticoid receptors. This class of transcription factors has a modular structure of distinct functional domains that can be swapped experimentally without significant loss of function (Kastner et al., 1990; Brosens et al., 2004). PR-A and -B are transcribed from the same gene on chromosome 11 by alternative promoter usage (Kastner et al., 1990). The resultant transcripts generate two proteins that differ in size with PR-B containing an additional 164 amino acids at the amino terminus. Close analysis of the PR gene has revealed the potential for multiple protein products generated by alternative transcription, translation, or splicing. There has been speculation about the functional relevance of alternative transcripts such as PR-C, PR-M and PR-S, although the existence and physiological relevance of these isoforms remain controversial (Samalecos and Gellersen, 2008).

While the DNA and hormone binding affinities of PR-A and -B are indistinguishable, their transcriptional actions are remarkably divergent. Early experiments on reporter constructs of simple or complex progesterone response elements (PREs), suggested that PR-A displays very little intrinsic transcriptional activity and acts primarily as a dominant inhibitor of PR-B and other steroid hormone receptors (Vegeto et al., 1993). It is now clear that PR-A and PR-B govern distinct networks of target genes in a cell-specific context (Richer et al., 2002). Unequivocal support for this notion came from selective gene knockout studies in mice, demonstrating that PR-A is indispensible for ovarian and uterine functions whilst PR-B is obligatory for mammary gland development (Conneely et al., 2002; Mulac-Jericevic et al., 2003). Thus PR-A is likely to be the dominant receptor isoform in both endometrium and myometrium.

Ligand binding is thought to occur at PRs anchored in cytoplasmic multi-subunit protein complexes consisting of variable heat shock proteins (p23, HSP70, HSP40 and HSP90) and the immuophilins FKBP51 and FKB52 (Kosano et al., 1998; Tranguch et al., 2007). The assembly of PR with these macromolecular complexes plays a key role in both the dynamic trafficking of the receptor and the maintenance of an active pool of protein ready to receive freely diffusing P4 from the circulating plasma binding protein transcortin. Once bound to P4, the subsequent conformational change in PR promotes dissociation from the chaperone scaffold, followed by homologous dimerization prior to translocation to the nucleus. In the nucleus, activated PR binds to specific nucleotide recognition sequences in promoters of target genes, leading to recruitment of chromatin-modifying co-repressor or -activator complexes, and finally transcriptional repression or activation, respectively (Brosens et al., 2004).

This 'classical' model of action predicts that response to P4 signaling should be proportional to the cellular abundance of PR and associated binding proteins. Evidence in endometrial cells during the decidualization process demonstrates that this is emphatically not the case. Despite the presence of abundant PR in primary endometrial cells, exposure to P4 triggers the expression of few, if any, genes (Aghajanova et al., 2011). Although initially difficult to reconcile with the fact that decidualization is a P4 dependent process *in vivo*, subsequent experiments demonstrated that sustained activation of the protein kinase A (PKA) pathway is required to sensitize endometrial cells to P4 (Brosens et al., 1999; Gellersen and Brosens, 2003; Jones et al., 2006). The endometrial response to rising P4 during the secretory phase of the cycle is therefore preceded by the rising intracellular cAMP levels and PKA activation, which in turn induces a diverse array of transcription factors including C/EBPα, STAT5 and FOXO1 (Gellersen and Brosens, 2003). It seems likely that the recruitment of these transcription factors into the PR dependent transcriptional complex is necessary for the classical P4 decidualisation response. Importantly, because cAMP levels are under the control of exogenous factors such as prostaglandin E2, corticotropin releasing factor and relaxin, the P4 response in decidualizing endometrium is both cell and environment specific.

As previously alluded to, nuclear receptors such as PR do not have the intrinsic ability to modify chromatin structure to allow access of the transcriptional machinery to DNA (Lonard and O'Malley, 2006; Han et al., 2009; Thakur and Paramanik, 2009). The required modifications are made by recruitment of co-regulators that possess histone and DNA modifying activity. The number of known co-regulator proteins, which can either promote or inhibit transcription now exceeds 300 (Onate et al., 1995; Thakur and Paramanik, 2009), and their defined roles in regulating PR transcription in the endometrium requires further investigation.

Once formed, assembled transcription factor complexes containing PR are capable of initiating gene transcription at other, sequence-specific, transcription factor sites. Such cross-talk is critical to the cAMP dependent decidualisation response and is dependent on the binding partners p53, FOXO1, HOXA10, HOXA11, STAT5 and C/EBPβ (Christian et al., 2002a; 2002b; 2002c; Mak et al., 2002; Pohnke et al., 2004; Schneider-Merck et al., 2006; Lynch et al., 2009; Christian et al., 2011). Since PR-A is essential for decidualization it seems likely that it acts as a critical scaffold protein upon which transcription factor complexes are assembled to transcribe a cohort of decidua specific genes. Such complexes are not limited to genes containing PR binding elements (PREs) or to ligand bound PR. The PR has been demonstrated to modulate Activator Protein 1 (AP1), Nuclear Factor-KappaB (NF-κB) and Specificity Protein 1 (SP1) transcriptional activity thus expanding the transcriptional network beyond PRE containing genes (Bamberger et al., 1996; Kalkhoven et al., 1996; Owen et al., 1998) and independent of P4 (Cloke et al., 2008).

A final layer of complexity in PR signalling in endometrium comes from posttranslational modifications of the receptor. These modifications (phosphorylation, sumoylation, ubiquitination, and acetylation) are rapid and dynamic and provide a means to fine tune PR signalling in the context of complex environmental signals (Brosens et al., 1999; Lange et al., 2000; Abdel-Hafiz et al., 2002; Jones et al., 2006; Daniel et al., 2010; Leitao et al., 2010). The consequences of modification are many-fold and can involve changes in sub-cellular localisation, protein stability, targeted degradation in the proteasome, altered interactions with co-factors and/or target gene expression. A well-defined example of a physiologically important modification in the reproductive tract is the suppressive effect of sumoylation on transcriptional activity of PR-A (Jones et al., 2006). This sumoylation dependent suppression is potently stimulated by oxidative stress in endometrial cells, but is selectively disabled during the process of decidualisation, thus emphasising the context dependence of posttranslational modifications (Leitao et al., 2010; 2011).

Much of the evidence of PR action in the decidua is provided from studies on decidualisation during the menstrual cycle, implantation and early support for pregnancy prior to establishing the placenta. Relatively less well studied is the role of decidua during late pregnancy and in particular potential roles for the decidua in initiating parturition.

## The role of the decidua in the onset of labor

There is abundant evidence from different species that the decidua is a major source of prostaglandins at term (Keelan et al., 2003; Olson, 2003). Consequently, the decidua may play a role in determining the length of gestation. Recent genetic studies in mice demonstrated that increased decidual prostanoid production precipitates preterm labor in the absence of P4 withdrawal, a prerequisite for term parturition in this species. Interestingly this effect could be triggered by genetic alteration of two distinct pathways. Uterine-specific deletion of p53 was sufficient to induce decidual senescence, increased Akt signalling, prostaglandin-endoperoxide synthase 2 (Ptgs2), prostaglandin F synthase and consequently greater production of the uterotonin PGF2α (Hirota et al., 2010). This effect is mediated by mammalian target of rapamycin complex 1 (mTORC1) and is reversed by low doses of the mTORC1 inhibitor rapamycin (Hirota et al., 2011). The same phenotype (*i.e.* preterm birth in the absence of progesterone withdrawal) is induced in mice hypomorphic for the prostaglandin-degrading enzyme 15-hydroxyprostaglandin dehydrogenase (15-HPGD) (Roizen et al., 2008). Thus, increased prostanoid synthesis, or decreased degradation, in the decidua is sufficient to trigger preterm birth in a species normally reliant on progesterone withdrawal for parturition. This effect can be replicated upon administration of other agonists, such as oxytocin (OT), in either wild-type or OT-deficient mice where the threshold for stimulus is lower in KO mice (Imamura et al., 2000).

These observations suggest that a complex relationship between uterine sensitivity and the magnitude of stimulation determines the timing of labor. It is clear that P4 regulates uterine sensitivity to stimulation (see infra) but it is much less obvious if it also regulates the level of stimulation *per se*. (Roizen et al., 2008). The question that arises is how this change in sensitivity and stimulation is achieved in species such as humans that do not depend on falling P4 levels to initiate labor. There is a set of experimental observations that potentially shed light

on the role of PR in modulating these thresholds in different species.

There is a clear difference in the efficacy of PR antagonists to induce labor between species that normally deliver in the presence of high P4 and those that exhibit systemic P4 withdrawal. In the latter, administration of RU486 (mifepristone), a mixed PR/GR antagonist, is sufficient to trigger preterm parturition (Chwalisz, 1994). This contrasts to species that normally deliver in the presence of high circulating P4 levels. Administration of RU486 here leads to an increased uterine sensitivity and cervical ripening but induction of labor requires co-administration of oxytocics (e.g. oxytocin or prostaglandins). In contrast, the pure PR antagonist onapristone precipitates labor without the need for oxytocics, although only when administered during mid-to-late gestation but not earlier (Elger et al., 1986; 1987). The effect of onapristone is PR-specific and reversible by co-administration of the PR agonists R5020 or gestodene (Chwalisz et al., 1995). The reason for the discrepancy in the actions of onapristone and RU486 is not understood but may be related to the high cAMP/PKA activity in the decidua, which converts RU486 into a partial PR agonist (Nordeen et al., 1993). If so, these observations suggest that the gestation-dependent increase in oxytocic drive may emanate from the decidua/fetal membranes in species lacking systemic P4 withdrawal. For example, it is possible that decidual senescence, associated with increased prostaglandins production and/or loss of prostaglandin dehydrogenase activity, could be a predetermined process that is timed relative to the implantation process.

## The myometrium and onset of labor

The majority of gestation is characterized by a dominance of uterine quiescence, whereby the growing fetus develops in a safe uterine environment until a point sufficient for extra-uterine survival. It is generally accepted that prior to the onset of labor the myometrium undergoes a process of 'activation' (Challis et al., 2000) whereby the muscle becomes more electrically excitable and susceptible to stimulation by pro-contractile hormones. This process is mediated by the increase in expression of certain contraction associated protein (CAP) genes (e.g. oxytocin receptor (OXTR), prostaglandin endoperoxidase synthase 2 (PTGS2), connexin 43 (GJA1) *etc*.), concomitant changes is resting membrane potential (Parkington, Tonta et al. 1999), and a decrease in cAMP/PKA activity (Dodge et al., 1999).

Cumulative evidence from different mammalian species indicates that only some labor-associated myometrial changes are mediated directly by P4. As mentioned, administration of RU486 or onapristone leads to increased myometrial responsiveness in all species tested so far, irrespective of the time in gestation (Chwalisz and Garfield, 1994). The observed increase in uterine responsiveness occurs for both OT and prostaglandins and is not mediated by an increase is receptor number (Elger et al., 1986; Chwalisz et al., 1991; Chwalisz, 1994). The fact that increased uterine responsiveness prior to parturition is not accounted for by an increase in either ligand or receptor suggests that a more fundamental change in electrophysiological properties of the myometrium may underpin this phenomenon.

The central process that governs uterine contractions is the generation of electrical activity in the form of complex action potentials that mediate voltage-gated calcium entry and hence contractions (Blanks et al., 2007). The spread of electrical activity throughout the uterine smooth muscle is critically dependent on the formation of electrical synapses by gap junction proteins between cells (Garfield et al., 1977; 1978; 1988). An increase in cell coupling would render the uterus much more sensitive to stimulation by dramatically increasing the efficacy of oxytocics to trigger membrane depolarization (Blanks et al., 2007). This is certainly true for OT. While the uterus is sensitive to picomolar concentrations of OT *in vivo*, the binding affinity of OT for its receptor is much higher (1nM) (Blanks, 2003). Thus, coupling intracellular calcium release to a tissue level action potential and voltage gated calcium entry enables OT to elicit a full agonist response with comparatively low receptor occupancy. Consistent with this hypothesis, administration of anti-progestins in rats and guinea pigs dramatically increases gap junction proteins at the plasma membrane of uterine myocytes (Garfield et al., 1987; Chwalisz et al., 1991). In addition to gap junction proteins, PR regulates the expression of the main pore forming subunit of the voltage-gated L-type calcium channel, further intimating that P4 modulates uterine excitability (Chwalisz et al., 1995).

The observation that most mammalian species initiate parturition in response to falling circulating progesterone levels combined with the fact that PR antagonists universally increase myometrial responsiveness to uterotonics underpin the widely held view that local P4 withdrawal must trigger the onset of labor in humans. In fact, numerous mechanisms of local P4 withdrawal have been proposed, focusing either on modulation of PR function, P4 metabolism, and/or P4-dependent suppression of inflammation (Mendelson, 2009; Mesiano et al., 2011). None of these mechanisms are necessarily mutually exclusive and yet - in our view –conclusive proof that local P4

withdrawal is obligatory for labor is as yet lacking. It is indeed striking that P4 therapy is effective in the prevention of preterm labor in some but not all women (da Fonseca et al., 2003; Meis et al., 2003; Fonseca et al., 2007).

A popular concept is that a change in the ratio of PR isoforms accounts for local P4 withdrawal in the myometrium. This is based on the observation that myometrial biopsies taken during labor express relatively more PR-A than PR-B when compared to samples obtained prior to labor (Merlino et al., 2007). Further, an increase in PR-A/PR-B ratio in an immortalized myometrial cell line has been shown to activate pro-inflammatory genes (Tan et al., 2012). While attractive, the *in vivo* relevance of these observations remains difficult to test as a change in PR-A/B ratio cannot underpin labor in mice (the usual *in vivo* model) as gestation and parturition are unperturbed upon PR-B silencing. The hypothesis is pertinent to those species that do not exhibit systemic P4 withdrawal, although the model fails to explain the requirement for oxytocics to induce labor upon treatment with PR antagonists.

A related hypothesis is predicated on the observation that P4 and inflammatory signalling pathways are closely intertwined and converge on the reciprocal inhibitory interaction between PR and the NF-κB transcription factor complex. For example, P4 has been shown to inhibit binding of the NF-κB-p65 complex to response elements in the *PTGS2* promoter (Hardy et al., 2006), a process that may be mediated through physical interaction between p65 and the activated PR (Kalkhoven et al., 1996). P4 also stimulates the expression of the binding protein IκBα responsible for maintaining NF-κB in a transcriptionally inactive state in the cytosol (Hardy et al., 2006). This model assumes that the inhibitory effects of P4 are overridden in response to increased NF-κB activation, which in turn establishes a positive feedback mechanism by decreasing P4-mediated repression. In support of this notion, increased NF-κB activity has been shown to decrease the expression of PR co-activators, thus diminishing receptor activity (Condon et al., 2003). However, a recent study using primary human myocytes indicated that NF-κB activation interferes only with the ability of the PR to activate but not repress target genes (Lee et al., 2012). Further, and in contrast to observations in an immortalized cell line, P4 did not inhibit the inflammatory response in primary cultures.

A final proposed pathway for P4 withdrawal, which may be complimentary to the mechanisms proposed for PR, is a local metabolism of P4. The onset of labor in mice is associated with striking non-labor phenotypes in knockouts of the P4 metabolizing enzyme 20α-hydroxysteroid dehydrogenase (20α-HSD) and 5α-reductase type 1 (Mahendroo et al., 1996; 1999; Piekorz et al., 2005; Ishida et al., 2007). In a species that normally experiences systemic P4 withdrawal these interesting phenotypes suggest that P4 clearance from uterine tissues is also important. Interestingly, recent evidence suggests that 20α-HSD may be regulated in the uterus by STAT5b, which itself is under the regulation of miR200a(Williams et al., 2012). Furthermore, miR-200a is up regulated at term in mice and humans and is also capable of regulating the E-box binding homeobox proteins ZEB1 and ZEB2 (Renthal et al., 2010). These transcription factors also regulate the oxytocin receptor (OXTR) and connexin-43 (CX43) in a PR dependent manner. Thus, P4 metabolism and PR transcriptional activity may be co-regulated to create a concerted alteration in the P4 response.

## Perspective

It is clear that there is much work still to be done before we can establish exact mechanisms of P4 and PR action in the myometrium throughout gestation and prior to parturition. Of particular importance is the need to reconcile data obtained from various *in vitro* systems and cell lines with *in vivo* observations, for example in response to PR antagonists. Furthermore, the role of PR action in late gestation in the decidua requires greater focus as relatively little is known compared to our understanding of the role of this nuclear receptor during menstrual cycle. It seems highly probable that a focus on the juxtacrine interactions between uterine compartments may yield a better understanding of the role of P4 in both term and preterm labor.

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