

A review of progesterone roles in implantation

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ABSTRACT

Implantation failure constitutes one of the major causes of pregnancy loss in all mammalian species. The complexity of implantation mechanism involves series of hormones, macromolecules, cytokines, chemokines, growth factors and repertoire of genes, however, progesterone receptor through which physiological responses to progesterone are initiated is the most essential for implantation across all mammalian species. Progesterone is also known as hormone of pregnancy because of its crucial roles to establish and sustain pregnancy and implantation. Progesterone facilitates blastocyst implantation to the maternal endometrium by promoting uterine secretion for conceptus growth and development, initiating window of receptivity, inducing quiescence and non-contraction of endometrium to avoid abortion and protection of embryo against maternal immune system. The aforementioned roles of progesterone and their mechanisms are the subject matter of this review.

Keywords: Blastocyst, endometrium, implantation, mammals, progesterone, progesterone receptor.

INTRODUCTION

For a successful pregnancy, a blastocyst must implant into a receptive endometrium. The process is complex and requires progressive interactions between both the maternal endometrium and embryo. Every viable embryo is destined to implant and towards this endeavour, the embryo attains implantation competence structurally and functionally. Embryo loss sequel to implantation failure is the major cause of reproductive wastage in cattle and livestock generally (Paria *et al.*, 2002). Implantation is a complex phenomenon that involves hormones, macromolecules, growth factors, glycocalyx, cytokines, chemokines, and extracellular matrix as well as repertoires of genes (Spencer *et al.*, 2008; van Mourik *et al.*, 2009; Altmäe *et al.*, 2010; Kim & Kim, 2017). The molecular mechanism underlying this phenomenon of implantation in mammals is so complex and complicated such that much are still desired to be known (Aplin, 2006). Of all candidate genes involved in mammalian embryo implantation, progesterone receptor (PR) is the most vital by stimulating expression of specific gene networks in different cell types (luminal and glandular epithelium, stroma, vascular cells and leukocytes) within the uterus and the

products of these genes implement the observed hormonal effects during early pregnancy (Bagchi *et al.*, 2003).

Progesterone, an ovarian steroid is a key component in the complex regulation of normal female reproductive capacities and functions. In mammalian females, the major physiological roles of progesterone include maturation of oocytes, ovulation, fertilization, embryo implantation, mammary gland development and the initiation of signals (in the brain) that brings about exhibition of sexual behaviour (Graham & Clarke, 1997). Cellular action of progesterone is mediated via PR. Progesterone receptor knockout (PRKO) female mice exhibit various reproductive abnormalities such as impaired gonadotrophins regulation, anovulation, uterine dysfunction, defective embryo uterine implantation and altered mammary gland morphogenesis (Conneely *et al.*, 2001). Oestrogen receptor deficient mice also failed to implant due to inability of the tubular gland to form branches which facilitates their secretory function and expression of Leukemia inhibitory factor (Granger *et al.*, 2024), an essential factor for implantation process (Raheem, 2018).

In consonance with its central roles in female reproductive capacity and functioning, impaired progesterone response or its unnecessary prolongation has been implicated in a broad

spectrum of reproductive disorders including endometrial cancer, abnormal parturition, retained placenta, metritis and preterm labour in human and animal species (Royal *et al.* 2000; Ito *et al.*, 2007). Sequel to this is the therapeutic application of progestagens and their derivatives as well as antagonist in reproductive medicine, gynaecology and obstetrics (Chwalisz *et al.*, 2005).

Although, many studies have been done to elucidate the crucial role roles played by during pregnancy to an extent of tagging it as the 'hormone of pregnancy', it remains a persistent concern of reproductive biologists to understand the mechanisms underlying progesterone roles during implantation process in mammalian species for a better development of strategies necessary to deal with two major contrasting global issues of reproductive concern, namely, improving fertility on one hand and developing a novel contraceptive on the other hand. Therefore, the mechanisms through which progesterone promotes implantation in mammalian species were the subjects of this review.

METHODOLOGY

The preliminary search strategy involved using the United States National Library of Medicine (<https://www.ncbi.nlm.nih.gov/pubmed/>) to look for literatures on progesterone and implantation between October, 2023 to December, 2023. The inclusion criteria include the relevance of articles to the subject and having complete referencing. The plenty of papers generated were selected based on their relevance to the subject matter of this review by going through the titles and abstract. These were read one by one and key references from them were also examined to know papers to include and those to discard. Publications that weren't relevant to the subject or that had unverifiable information, out-dated references, insufficient referencing or duplicate material were excluded. Other relevant textbooks and summaries were also consulted and reviewed to generate a broad knowledge presented in the subsection below.

INITIATE WINDOW OF RECEPTIVITY

Window of receptivity is a period when the uterine environment is favourable to blastocyst attachment to the endometrium. Most of the acknowledge markers of endometrial receptivity such as mucin (MUC1), osteopontin and integrin expressed by the endometrium are all progesterone dependent (Lessey *et al.*, 1996; Johnson, 2001, Raheem *et al.*, 2018). MUC1 served as a protective covering of the endometrium against microorganism (Brayman *et al.*, 2004) and must be eliminated by a factor generated by the embryo (Raheem *et al.*, 2016) to facilitate interaction between the maternal endometrium and embryo leading to a successful implantation. Osteopontin also known as secreted phosphoprotein 1 is a secreted extracellular matrix protein of

endometrium and has been acknowledged as an adhesive molecule during implantation by the binding of its receptors at uterine luminal epithelium (LE) and conceptus trophoblast to attach the conceptus to the uterus during implantation (Johnson *et al.*, 2014). Among other variants of integrins, alpha-v beta-3 had the best predictive value for endometrial receptivity among biomarkers in the uterine fluid (Wang *et al.*, 2020). In human, co-expression of these glycoproteins (osteopontin and integrins, alpha-v beta-3) was observed during window of implantation (He *et al.*, 2016).

In assisted reproductive technologies, uterine receptivity represents the optimal time for embryo transfer. The success of embryo transfer depends much on the status of the endometrium at which the embryo is placed therein. Progesterone supplementation was reported to extend uterine receptivity for blastocyst implantation in mice (Song *et al.*, 2007). Progesterone is used to prepare the endometrium of the surrogate mother for embryo transfer (de Ziegler *et al.*, 1998), hypothesised on utero-relaxation of the endometrium, creating a conducive environment for implantation to occur.

UTERINE SECRETION FOR CONCEPTUS GROWTH AND DEVELOPMENT

In a conceptive cycle, the endometrial glands secrete arrays of hormones, growth factors, cytokines macromolecules and proteins collectively termed histotroph into the uterine lumen (Bazer, 1975). Histotroph is essentially required for embryo survival and is of particular importance for conceptus survival and growth in domestic animals due to the protracted period of peri-implantation and the superficial nature of implantation in this species (Spencer *et al.*, 2004). Osteopontin is a major component of the histotroph (Dunlap *et al.*, 2008) and is produced by uterine glands (Johnson *et al.*, 2003), with increase production associated with progesterone (Johnson *et al.*, 1999; Johnson *et al.*, 2000). Several studies have demonstrated the importance of histotroph to implantation in uterine gland knock out (UGKO) ewe model (Filant & Spencer, 2014; Gray *et al.*, 2006). Ovine UGKO ewe was generated from neonatal administration of progesterone that resulted in an adult endometrial phenotype with a characteristic absence of glandular epithelium (Gray *et al.*, 2000). Infertility in the UGKO ewe is premised on the inability of the endometrium to synthesise histotroph (Gray *et al.*, 2002).

QUIESCENCE OF REPRODUCTIVE TRACT

Uterine contraction is a physiological phenomenon that occurs during parturition and at much lower intensity during oestrus. Uterine contraction is a primary function of the myometrial muscles. The mechanism involves oestrogen, oxytocin, prostaglandins and their receptors as well as other contraction- associated regulators like calcium, actin and myosin filaments (Pehlivanoglu *et al.*, 2013). In contrast to

oestrogen, progesterone reduces the excitability of the reproductive so that during the luteal phase, the uterine environment is quiescent with loss of tone (Cable & Grider, 2023). At trans-rectal palpation, the luteal phase is recognisable by the feeling of uterine flaccidity as against the tonic state during the follicular phase in cow (Raheem *et al.*, 2019). The quiescence of the uterus is of particular importance during the pre-attachment stage of pregnancy when the embryo is free-floating in the uterus, hence very prone to expulsion on a slight contraction of the uterus. Besides, the quiescence of the uterus at the time of implantation is most conducive for attachment to occur. Progesterone appears to inhibit uterine excitability by a number of mechanisms. Progesterone (genomic) during the luteal phase is known to down-regulate the expression of oestrogen receptor α (ER α) and hence the oxytocin receptor that happened to be the key factors that bring out uterine contractility. This phenomenon is referred to as 'progesterone block' (Kasa-Vubu *et al.*, 1992). Progesterone block created in ovariectomised ewes injected by continued progesterone administration was reversed within 12 to 24 h after intrauterine administration of oestradiol-17 beta (Porter & Lye, 1983). Uterine contraction also involved the ionic concentration of calcium and potassium to generate the voltage potential and crosslinking of the actin and myosin filament (Aguilar & Mitchell, 2010). Studies have shown that progesterone affects these elements in a manner that causes uterine quiescence (Fomin *et al.*, 1999; Soloff *et al.*, 2011).

It is noteworthy that the quiescence of uterus during early pregnancy is not the same for all mammalian species. For instance, a level of uterine contraction is observed in pig and horse. Porcine embryos migrate between the uterine horns and elongate prior to uterine attachment (Johnson *et al.*, 2021). The maternal recognition of pregnancy in the sow is oestrogen (Raheem, 2017) which redirects the synthesis of luteolytic prostaglandin F_{2 α} away from endocrine to exocrine, away from the ovary into the endometrial lumen where it causes certain level of contraction.

Uterine tone which is partly responsible for the movement of embryo from one horn to another is a positive sign of pregnancy in mare (Bonafos *et al.*, 1994). This movement is postulated to sensitize the different region of the endometrium for implantation and restriction of embryo culminates into pregnancy termination (Raheem, 2017). In pig, contraction of myometrium of gravid pigs was reportedly higher than non-gravid (cycling) mates (Markiewicz *et al.*, 2016) and such contraction is hypothesised to cause even distribution of multiple embryos in the endometrial lumen of a gravid pig.

PROTECTION OF EMBRYO AGAINST MATERNAL IMMUNITY

Within the first two weeks of pregnancy, embryos of sheep, pig, goat, cow and most mammalian species exhibit maternal recognition of pregnancy to indicate their presence to the maternal endometrium (Roberts *et al.*, 1996). This implies that by this time, the maternal immune system could detect the embryo and if treated as a foreign body per se, abortion is very imminent. Several studies have shown down-regulation of the maternal immune system especially in the endometrium during early pregnancy. It is hypothesised that the maternal immune system is selectively down regulated under a progesterone-dominant endometrium as observed during the luteal phase compared with the follicular phase when the endometrium is under the influence of oestrogen (Ramadan *et al.*, 1997; Lewis 2003) since there are up-regulation of others.

A similar observation was seen in pigs (Wulster-Radcliffe *et al.*, 2003). In another perspective, progesterone was reported to facilitate release of prostaglandins E₂ (PGE₂), a strong immunosuppressant by the foetal macrophages (Yagel *et al.*, 1987) through inhibition or suppression of some certain proteins that include platelet aggregation and interleukins 5/13 production by innate lymphoid cells (ILCs), and by suppressing neutrophil, Natural Killer cells and monocyte effector functions (Andrade *et al.*, 2020). Krzymowski and Stefańczyk-Krzymowska (2012) proposed in their review that free progesterone in the maternal blood blocks the capacity of dendritic cells, macrophages and monocytes in the maternal reproductive tract from presenting embryonic antigens to T helper cells. Progesterone-induced blocking factor and galectins were reported to modulate maternal immune response during pregnancy (Okumu *et al.*, 2011).

CONCLUSION

Progesterone is essential for establishment of pregnancy and implantation by creating conducive endometrial milieu for conceptus survival via uterine secretion for nourishment of conceptus growth and development, quiescence of endometrium and moderating maternal immune system for protection of embryo. Progesterone also facilitates window of implantation, a term was first used by Edward in 1988 for human endometrium (Edwards, 1988) and is a major determinant of implantation success because a mature blastocyst can wait for a receptive endometrium but not vice versa (Dickmann & Noyes, 1960; Noyes & Dickmann, 1960).

In conclusion, understanding the progesterone mechanisms of action during implantation is essential for therapeutic usage of progesterone, progesterone derivatives or antagonist

to improve reproductive health in animal and human subjects by facilitating conception or developing contraception.

CONFLICT OF INTEREST

There was no conflict of interest.

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