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Review
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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-contractility of endometrium to avoid abortion and protection of embryo against maternal immune system. The aforementioned 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 (luminar 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

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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 Unites 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.,* 2017). 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 phospoprotein 1 is a secreted extracellular matrix protein of endometroim and has been acknowledged as an adhesive molecule during implantation by the binding of its receptors at uterine luminal epithelium (LE) and conceptus trophectoderm 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, 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 (Pehlivanoğlu 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 (ERα) 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, 2015) which redirects the synthesis of luteolytic prostaglandin $F_{2\alpha}$ 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, 2015). 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 (Lewis 2003; Ramadan *et al.*, 1997) 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 E_2, 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.

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CONFLICT OF INTEREST

There was no conflict of interest.

REFERENCES

Aguilar, H.N. & B.F. Mitchell (2010). Physiological pathways and molecular mechanisms
regulating uterine contractility. Human Reproduction Update, 16: 725-744.

Altmäe, S, J., A. Martínez-Conejero, A., Salumets, C Simón, J.A. Horcajadas & A. Stavreus-Evers (2010). Endometrial gene expression analysis at the time of embryo implantation in women with unexplained infertility. Molecular Human Reproduction, 16: 178-187.

Andrade, G. M., Vasquez Martinez, G., Perez-Campos Mayoral, L., Hernandez-Huerta, M. T., Zenteno, E., Perez-Campos Mayoral, E., Martinez Cruz, M., Martinez Cruz, R., Matias-Cervantes, C. A., Meraz Cruz, N., Romero Diaz, C., Cruz-Parada, E. & Perez-Campos, E. (2020). Molecules and Prostaglandins Related to Embryo Tolerance. Frontiers in Immunology, 11, 555414.

Aplin, JD (2006). Embryo implantation: the molecular mechanism remains elusive. Reproductive Biomedical Online, 13: 833-839.

Bagchi, IC, YP Cheon, Q Li & MK Bagchi (2003). Progesterone receptor-regulated gene networks in implantation. Frontiers in Bioscience, 8:852-861.

Bazer FW (1975). Uterine protein secretions: Relationship to development of the conceptus. Journal of Animal Science, 41: 1376-1382.

Bonafos, L. D., Carnevale, E. M., Smith, C. A. & Ginther, O. J. (1994). Development of uterine tone in nonbred and pregnant mares. Theriogenology, 42(8), 1247-1255.

Brayman, M., Thathiah, A. & Carson, D. D. (2004). MUC1: a multifunctional cell surface component of reproductive tissue epithelia. Reproductive Biology Endocrinology, 2:4

Cable, J. K. & Grider, M. H. (2023). Physiology, Progesterone: StatPearls Publishing, Treasure Island (FL)

Chwalisz K, Perez MC & WC Demanno D, Schubert G & Elger W (2005). Selective progesterone receptor modulator development and use in the treatment of leiomyomata and endometriosis. Endocrine Reviews, 26: 423-438.

Conneely OM, B Mulac-Jericevic, JP Lydon, and FJ De Mayo (2001). Reproductive functions of the progesterone receptor isoforms: lessons from knock-out mice. Molecular Cellular Endocrinology, 179: 97-103.

de Ziegler, D., Fanchin, R., de Moustier, B. & Bulletti, C. (1998). The hormonal control of endometrial receptivity: estrogen (E2) and progesterone. Journal of Reproductive Immunology, 39(1-2), 149-166.

Dickmann, Z. & Noyes, R. (1960). The fate of ova transferred into the uterus of the rat. Reproduction, 1(2), 197-212.

Dunlap KA, DW Erikson, RC Burghardt, FJ White, KM Reed, JL Farmer, TE Spencer, RR Magness, FW Bazer, KJ Bayless & GA Johnson (2008). Progesterone and placentation increase secreted phosphoprotein one (SPP1 or osteopontin) in uterine glands and stroma for histotrophic and hematotrophic support of ovine pregnancy. Biology of Reproduction, 79: 983-990.

Filant, J. & Spencer, T. E. (2014). Uterine glands: biological roles in conceptus implantation, uterine receptivity and decidualization. International Journal of Developmental Biology, 58(2-4), 107-116.

Fomin VP, BE Cox & RA Word (1999). Effect of progesterone on intracellular Ca2+ homeostasis in human myometrial smooth muscle cells. American Journal of Physiology - Cell Physiology 276: (2) C379-C385.

Graham JD & CL Clarke (1997). Physiological action of progesterone in target tissues. Endocrine Reviews, 18: 502-519.

Granger, K., Fitch, S., Shen, M., Lloyd, J., Bhurke, A., Hancock, J., Ye, X. & Arora, R. (2024). Murine uterine gland branching is necessary for gland function in implantation. Molecular Human Reproduction, 30(6).

Gray AC, FF Bartol, KM Taylor, AA Wiley, WS Ramsey, TL Ott et al., (2000). Ovine uterine gland knock-out model: effects of gland ablation on the estrous cycle. Biology of Reproduction 62: 448-456.

Gray CA, RC Burghardt, GA Johnson, FW Bazer & TE Spencer (2002). Evidence that absence of endometrial gland secretions in uterine gland knockout ewes compromises conceptus survival and elongation. Reproduction, 124: 289-300.

Gray, C. A., Abbey, C. A., Beremand, P. D., Choi, Y., Farmer, J. L., Adelson, D. L., Thomas, T. L., Bazer, F. W. & Spencer, T. E. (2006). Identification of endometrial genes regulated by early pregnancy, progesterone, and interferon tau in the ovine uterus. Biol Reprod, 74(2), 383-394.

He, Z., Ma, Y., Li, L., Liu, J., Yang, H., Chen, C., Lin, N., Bai, Y., Ma, R., Li, R., Wu, Z. & Qiao, J. (2016). Osteopontin and Integrin alphavbeta3 Expression during the Implantation Window in IVF Patients with Elevated Serum Progesterone and Oestradiol Level. Geburtshilfe Frauenheilkd, 76(6), 709-717

Ito K, H Utsunomiya, N Yaegashi & H Sasano (2007). Biological roles of estrogen and progesterone in human endometrial carcinoma-new developments in potential endocrine therapy for endometrial cancer. Endocrinology Journal, 54: 667-679.

Johnson GA (2001). Muc-1, Integrin, and osteopontin expression during the implantation cascade in sheep. Biology of Reproduction, 65: 820-828.

Johnson GA, RC Burghardt, MM Joyce, TE Spencer, FW Bazer, CA Gray & C Pfarrer (2003). Osteopontin is synthesized by uterine glands and a 45-kDa cleavage fragment is localized at the uterine-placental interface throughout ovine pregnancy. Biology of Reproduction, 69: 92-98.

Johnson GA, RC Burghardt, TE Spencer, GR Newton, TL Ott & FW Bazer (1999). Ovine osteopontin: II.

Osteopontin and alpha (v) beta (3) integrin expression in the uterus and conceptus during the periimplantation period. Biology of Reproduction, 61: 892-899.

Johnson GA, TE Spencer, RC Burghardt, KM Taylor, CA Gray & FW Bazer (2000). Progesterone modulation of osteopontin gene expression in the ovine uterus. Biology of Reproduction, 62: 1315-1321.

Johnson, G. A., Burghardt, R. C. & Bazer, F. W. (2014). Osteopontin: a leading candidate adhesion molecule for implantation in pigs and sheep. Journal of Animal Science Biotechnology, 5(1), 56.

Johnson, G. A., Bazer, F. W. & Seo, H. (2021). The Early Stages of Implantation and Placentation in the Pig. Advances in Anatomy, Embryology and Cell Biology, 234, 61-89.

Kasa-Vubu, J. Z., Dahl, G. E., Evans, N. P., Thrun, L. A., Moenter, S. M., Padmanabhan, V. & Karsch, F. J. (1992). Progesterone blocks the estradiol-induced gonadotropin discharge in the ewe by inhibiting the surge of gonadotropin-releasing hormone. Endocrinology, 131(1), 208-212.

Kim, S.-M. & Kim, J.-S. (2017). A Review of Mechanisms of Implantation. Development & reproduction, 21(4), 351-359.

Krzymowski T, and S Stefańczyk-Krzymowska (2012). Advances in understanding the physiological mechanism of maternal immune tolerance to the embryo. Reproductive Biology 12: 265-270.

Lessey BA, I Yeh, AJ Castelbaum, MA Fritz, AO Ilesanmi, P Korzeniowski, J Sun & K Chwalisz (1996). Endometrial progesterone receptors and markers of uterine receptivity in the window of implantation. Fertility and Sterility, 65: 477-483.

Lewis GS (2003). Role of ovarian progesterone and potential role of prostaglandin F2alpha and prostaglandin E2 in modulating the uterine response to infectious bacteria in postpartum ewes. Journal of Animal Science, 81: 285-293.

Noyes, R. W. & Dickmann, Z. (1960). Relationship of ovular age to endometrial development. Reproduction, 1(2), 186-196.

Marashi V & T Rulicke (2012). The Bruce effect in Norway rats. Biology of Reproduction, 86: 1-5.

Markiewicz, W., Bogacki, M., Blitek, M. & Jaroszewski, J. J. (2016). Comparison of the porcine uterine smooth muscle contractility on days 12-14 of the estrous cycle and pregnancy. Acta Veterinaria Scandanavica, 58, 20.

Okumu, L. A., Fair, T., Szekeres-Bartho, J., O'Doherty, A. M., Crowe, M. A., Roche, J. F., Lonergan, P. & Forde, N. (2011). Endometrial expression of progesterone-induced blocking factor and galectins-1, -3, -9, and -3 binding protein in the luteal phase and early pregnancy in cattle. Physiol Genomics, 43(14), 903-910.

Paria BC, J Reese, SK Das & SK Dey (2002). Deciphering the cross-talk of implantation: advances and challenges. Science, 296: 2185-2188.

Pehlivanoğlu, B., Bayrak, S. & Doğan, M. (2013). A close look at the contraction and relaxation of the myometrium; the role of calcium. Journal of the Turkish German Gynecological Association, 14(4), 230.

Porter DG & SJ Lye (1983). Partial reversal of the myometrial progesterone 'block' in the non-pregnant ewe in vivo by oestradiol-17 beta. Journal of Reproduction and Fertility, 67: 227-234.

Raheem, K. A. (2015). An insight into maternal recognition of pregnancy in mammalian species. Journal of the Saudi Society of Agricultural Sciences, 16, 1-6.

Raheem, K. A., Wahab, Y. A., Raji, L.O. and Leigh, O.O. . (2019). Trans-Rectal Palpation- An Appraisal of Its Teaching In Nigerian Veterinary Schools. Savannah Veterinary Journal, 2(2), 44-49.

Raheem, K. A. (2018). Cytokines, growth factors and macromolecules as mediators of implantation in mammalian species. International Journal of Veterinary Science and Medicine, 6(Suppl), S6-S14.

Raheem, K. A., Marei, W. F. A., Campbell, B. K. & Fouladi-Nashta, A. A. (2016). In vivo and in vitro studies of MUC1 regulation in sheep endometrium. Theriogenology, 85(9), 1635-1643.

Ramadan AA, GL Johnson & GS Lewis (1997). Regulation of uterine immune function during the estrous cycle and in response to infectious bacteria in sheep. Journal Animal Science, 75: 1621-1632.

Roberts RM, S Xie & N Mathialagan (1996). Maternal recognition of pregnancy. Biology Reproduction, 54: 294-302.

Royal M, GE Mann & Flint AP (2000). Strategies for reversing the trend towards subfertility in dairy cattle. Veterinary Journal, 160: 53-60.

Soloff MS, YJ Jeng, MG Izban, M Sinha, BA Luxon, SJ Stamnes & SK England (2011). Effects of progesterone treatment on expression of genes involved in uterine quiescence. Reproductive Science, 18: 781-797.

Song H, K Han & H Lim (2007). Progesterone supplementation extends uterine receptivity for blastocyst implantation in mice. Reproduction, 133: 487-493.

TE, GA Johnson, FW Bazer & RC Burghardt (2004). Implantation mechanisms: insights from the sheep. Reproduction, 128: 657-668.

Spencer, T.E., O. Sandra & E, Wolf (2008). Genes involved in conceptus–endometrial interactions in ruminants: insights from reductionism and thoughts on holistic approaches. Reproduction, 135: 165-179.

Spencer TE, GA Johnson, FW Bazer & RC Burghardt (2004). Implantation mechanisms: insights from the sheep. Reproduction, 128: 657-668.

van Mourik MSM, NS Macklon & CJ Heijnen (2009). Embryonic implantation: cytokines, adhesion molecules, and immune cells in establishing an implantation environment. Journal of Leukocyte Biology, 85: 4-19.

Wang, L., Lv, S., Mao, W., Pei, M. & Yang, X. (2020). Assessment of endometrial receptivity during

implantation window in women with unexplained infertility. Gynecology Endocrinology, 36(10), 917-921.

Wulster-Radcliffe MC, RC Seals & GS Lewis (2003). Progesterone increases susceptibility of gilts to uterine infections after intrauterine inoculation with infectious bacteria. Journal Animal Science, 81: 1242-1252.

Yagel, S.A, Hurwitz A, B Rosenn & N Keizer (1987). Progesterone enhancement of prostaglandin E2 production by fetal placental macrophages. American Jornal Reproductive Immunology Microbiology, 14: 45-48.