Maternal recognition of pregnancy in some domestic animals: A review

**ABSTRACT**

**Introduction:** Maternal Recognition of Pregnancy (MRP) is a physiological process whereby the conceptus signals its presence to the maternal organism and prolongs the lifespan of the corpus luteum. MRP is critical to homeostasis of pregnancy. Many cases of pregnancy losses have been attributed to the failure of MRP. One of such cases is early embryonic mortality, a leading cause of infertility in animals. The purpose of this review is to highlight the general mechanisms of MRP and the species-specific differences in some domestic animals.

**Method:** A search was conducted with the exploration and filtration of databases and repositories of Google Scholars, Scopus, PubMed and ResearchGate for scientific publications.

**Results:** This article explains mechanisms of MRP in different domestic species of animals.

**Significance:** The concept would provide a better insight in understanding a major aetiology to pregnancy losses, which has an implication on production and the agrarian economy.

**Keywords:** Maternal recognition of pregnancy, Conceptus, Corpus luteum, Pregnancy loss.

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**Maternal recognition of pregnancy in some domestic animals: A review**

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mother and the foetus are not separated by an intact layer of epithelial cells, and placental trophoblast cells are thus exposed to maternal immune cells. A bidirectional transfer of cells between mother and foetus is common during human and murine pregnancy (Nelson et al., 2007).

A hypothesis proposed that the conceptus lacked immunogenicity, has been disputed because immune reactions against foetal cells have been described (Elbe-Burger et al., 2000). More recently, studies have shown that foetal tissue expresses major histocompatibility complex (MHC) molecules which are needed for immune recognition and activation (Bainbridge, 2000; Moffett and Loke, 2006; Erlebacher, 2013). All together, these findings showed that the conceptus had immunogenic properties. More so, there is ample evidence that pregnancy is recognized by the immune system. Antibodies against foetal antigens have been detected in the sera of pregnant women showing that maternal recognition of foetal antigens does occur (Billington, 1992). Women undergoing normal pregnancy preferentially release type 2 helper T cell (Th2) cytokines, whereas women who have recurrent spontaneous abortions induce the production of type 1 helper T cell (Th1) cytokines (Raghupathy, 1997). Thus, the maternal immune system does not only recognize pregnancy, but responds in a way to determine the fate of pregnancy.

The fourth hypothesis was advanced byBillingham (1964). BBillingham proposed that the uterus may be an immune privileged site, where foetal tissue directs the maternal immune response towards a protective, tolerant one. The concept of immune-privileged sites has been recognized by immunologists. Previous research by Dutch ophthalmologist, Van Dooremaaland observed prolonged survival of a mouse skin graft placed into the anterior chamber of a dog’s eye (Stein-Streileinand Streilein, 2002). The other tissues with the characteristics of immune-privileged sites include brain, ovary, testis, gravid uterus and placenta. These tissues are thought to avoid immune reactions by setting up anatomical and or physiological barriers, which prevent access to cells of the immune system (Trowsdale and Betz, 2006). Experimental evidences have also shown that transplant immunity can be both elicited and expressed in a normal manner in the uterus. The possibility of ectopic pregnancies demonstrates that the uterus does not uniquely protect the conceptus as an immune privileged site (Billington, 2003).

Evidence detailing the production of various hormones, proteins and cytokines by the placenta has expanded our knowledge on mechanisms by which uterine tissue functions as well as the putative roles of these hormones and cytokines in MRP (Petraglia et al., 1996; Smith et al., 2018). Some of the recent mechanisms put forward to explain the concept of MRP are:

Mechanosensation

Studies have shown that small intrauterine devices (water-filled plastic ball with a diameter of 20 mm) induce prolonged luteal function in the mare (Nie et al., 2003; Rivera Del Alamo et al., 2008; LeBlanc, 2011), supporting the concept of pregnancy recognition through mechanosensation. The hypothesis that an (intrauterine devices) IUD might achieve luteostasis through mild inflammation of the endometrium could not be reaffirmed. It was suggested that the close contact to or pressure of an IUD on the uterine wall may induce changes in the endometrial cells and therefore prevent them from releasing luteolytic pulses of PGF2α (Newcombe and Peters, 2014). Mechanosensation has also been reported to play a role in reproduction in other mammals. As exemplified in humans, an initial contact between the blastocyst and maternal tissues is by adhesion of the trophoblast to the uterine epithelium. This event is hormonally regulated and requires a certain degree of homeostatic pressure between the cell surfaces (Thie et al., 1998). Furthermore, a recent study in sheep has also described changes at the maternal-conceptus interface and uterine wall during pregnancy, which reflects an increased mechanosensation or mechanotransduction (Burghardt et al., 2009).

Progesterone

Among the important hormones present in maternal serum, progesterone (pro gestational hormone) appears to play a major role in reducing the maternal response to the foetal allograft (Beagley and Gockel, 2003). It is a well-known fact that progesterone is essential in the maintenance of pregnancy in a number of mammalian species. In humans, progesterone is produced solely by the placenta alone at high levels (Szekeres-Bartho, 2002). Early studies showed that high concentrations of progesterone can prolong the survival of allogeneic grafts (Szekeres-Bartho, 2002; Majewski and Hansen, 2002; Ajayi et al., 2012; Maillo et al., 2014). For example, Hansen et al. (1986) studied the effect of progesterone on skin transplants placed in the uterine lumen of ovariecotomized ewes. Allografts placed in the uterine lumen of progesterone treated ewes were present 30 days after engraftment while allografts placed in control animals were completely resorbed. Other studies have shown that progesterone can affect various phases of the immune response in vivo. Progesterone concentrations which mimic the high intrauterine concentration in pregnancy have been shown to effectively block cellular immune responses both in vitro and in vivo (Siiteri et al., 1977). Research has also shown that (using human blood cultures) progesterone was capable of inhibiting monocyte dependent T cell activation (Stites et al., 1983). Progesterone can induce its immunological changes by a number of cellular and molecular mechanisms. These mechanisms include stimulation of the activity of specific enzyme matrix metalloproteinases and adhesion molecules, inhibition of antibody production and suppression of T-cell activation and cytotoxicity. Modification of the activity of natural killer cells and induction of the secretion of protective asymmetric antibodies (Kyurkchiev et al., 2010).

The biological effects of progesterone during pregnancy are manifested by a 34kDa protein, called the Progesterone Induced Blocking Factor (PIBF), which is released by lymphocytes of pregnant animals following binding of progesterone to its receptors (Szekeres-Bartho, 2002). In pregnant animals, the PIBF concentration gradually increases until the 37th week of gestation, followed by a slow decrease until term. PIBF has been shown to...
alter the cytokine balance resulting in a preferential production of Th2 type cytokines in mice, inhibit NK cell activity through mediation by cytokines, and regulate anti-apoptotic effects (Szekeres-Bartho and Wegmann, 1996; Szekeres-Bartho, 2002; Kozma et al., 2006; Szekeres-Bartho et al., 2008). In a previous research it was found that peripheral blood of healthy pregnant animals had significantly higher (in all trimesters of pregnancy) percentage of PIBF positive lymphocytes than in animals at risk for premature pregnancy termination (Szekeres-Bartho et al., 1995).

Corticotropin Releasing Hormone (CRH) and its regulation of FasL expression

The CRH is a 41 amino acid peptide hormone that acts as the main neurotransmitter orchestrating the stress response through the secretion of adrenocorticotropic hormone (ACTH) from corticotropes of the anterior pituitary (McLean and Smith, 2001). In the same vein, it functions in the hypothalamic-pituitary-adrenal axis. Expression of CRH has been recognized at several different sites, including the placenta (McLean and Smith, 2001). The CRH appears to have a range of functions in the placenta and foetal membranes. These functions include the regulation of trophoblast cell growth and invasion, tissue remodelling, control of placental vascular tone through the activation of the nitric oxide pathway, direct modulation of endocrine function, especially prostaglandin generation and bioavailability, gestation length and bringing forth the onset of labour (Gammatopoulos, 2008). Furthermore, CRH is also known to have immunological effect. Traditionally hypothalamic CRH has been considered to act indirectly in an anti-inflammatory fashion as the end product of the hypothalamic-pituitary-adrenal axis is cortisol which is a well-known anti-inflammatory compound. However, CRH produced at peripheral inflammatory sites has been shown to possess potent pro-inflammatory properties that can influence both innate and acquired immune responses (Kalantaridou et al., 2007). In the reproductive system, intrauterine and ovarian CRH can have pro-inflammatory properties. For the intrauterine CRH, various studies have shown that it may participate in the acute aseptic inflammatory response that is characteristic of embryo implantation (Makrigiannakis et al., 2001, Brooks et al., 2014). The ovarian CRH can also participate in the inflammatory processes of ovulation and luteolysis (Kalantaridou et al., 2007). However, following implantation, the embryo suppresses the inflammatory response and prevents immune rejection. It has been hypothesized that the anti-inflammatory role of CRH may play a role in this process through interactions with the pro-apoptotic cytokine; Fas Ligand (FasL) (Makrigiannakis et al., 2001).

FasL is a type II membrane protein of approximately 280 amino acids that belongs to the TNF superfamily. FasL has a high level of conservation amongst species and is highly expressed on several immune cells including activated T and B lymphocytes, NK cells, monocytes and macrophages. The major function of FasL is to induce apoptosis in cells which express its receptor, Fas (Lee and Ferguson, 2003). The Fas-FasL system is involved in apoptosis and is extensively used by the immune system during lymphopoiesis and immunopoiesis. It is also a major mechanism during clonal deletion of autoimmune cells inside the central and peripheral lymphoid organs and is involved in the cytolytic pathways of NK cells, Th1 cells and cytotoxic T cells. The Fas/FasL system is also implicated in the regulation of cellular turnover, tumour cell elimination, antiviral responses and protection of particular tissues against potential danger represented mainly by activated lymphocytes (Houston and O’Connell, 2004). During pregnancy, FasL is expressed on the trophoblast and decidualized endometrial cells (Makrigiannakis et al., 2004; Taylor et al., 2006). Studies on placental exosomes have also shown the presence of cytoplasmic microvesicular forms of FasL in syncytiotrophoblast (Frangsmyr et al., 2005) and its secretion into maternal blood (Taylor et al., 2006). As a result of this expression profile, FasL has been speculated to have a role in embryo implantation and maternal immune tolerance.

Comparative aspect of maternal recognition of pregnancy

The processes leading to maintenance of pregnancy after successful fertilization and implantation of the developing conceptus into the uterine wall are species-specific. It seems that each species has a different pathway to prevent demise of the primary CL. For example, in ruminants, conceptus-derived interferon τau (Bazer et al., 1997), and in pigs, oestrogen, are critical for establishing pregnancy (Geisert et al., 1990). MRP is a reciprocal process involving both the embryo and the uterine environment.

Maternal recognition of pregnancy in the horse

In the mare, a primary CL formed at the time of conception is the only source of progesterone for at least the first month of pregnancy. In non-pregnant mares, luteolysis is triggered by an oxytocin-dependent pulsatile release of PGF2α from the endometrium between days 13 and 16 after ovulation (Ginther et al., 2008). Unlike in ruminants or pigs, PGF2α is thought to reach the ovaries of the mare only via the peripheral circulation where it promptly exerts its luteolytic effect. However, in the presence of a conceptus, the cyclical release of luteolytic PGF2α is suppressed to maintain a viable CL (Sharp, 2000). Co-incubation of conceptus membranes with endometrial tissue has been shown to block PGF2α production in vitro (Watson and Sertich, 1989) and measurements of PGF2α concentrations in uterine flushing recovered from cyclic mares reached high values during days 14–16 after ovulation, the expected time of luteolysis, but were negligible in pregnant mares at this time (Stout and Allen, 2001). The conceptus must therefore somehow prevent production of PGF2α as it traverses the uterus. However, the embryonic signal by which luteostasis is achieved in the mare still remains fully unknown.

Oxytocin is thought to play a central role in luteal regression in the mare. Oxytocin is a nonapeptide hormone produced mainly by the hypothalamic magnocellular neurons. It is stored in secre-
tory vesicles of the posterior pituitary along with its “carrier protein” neurophysin and released into the peripheral circulation in a pulsatile manner during the oestrous cycle (Vanderwall et al., 1998). Besides this classical hypothalamo–neurohypophysial axis, oxytocin has also been reported to be produced by other organs such as the ovary, placenta or testis (Fleming et al., 2006). In contrast to ruminants, the ovary of the mare does not appear to be a source for oxytocin during the oestrous cycle (Stevenson et al., 1991). However, it is of interest that, like in the pig, locally synthesized uterine oxytocin implicated an important role in control of cyclical luteolysis in the mare (Stout et al., 2000). Oxytocin-mRNA has been identified in the equine endometrium and oxytocin has been detected in secretory vesicles of the secretory (non-ciliated) cells of the uterine luminal and glandular epithelium. It is thought that secretion occurs in the intrauterine lumen, where it binds to its receptor on luminal epithelial cells and thereby stimulates the pulsatile release of PGF$_{2\alpha}$ leading to luteolysis (Stout et al., 2000, Bae et al., 2003). Furthermore, it has been demonstrated that the response of PGF$_{2\alpha}$ to oxytocin is maximal at the time of luteolysis in non-pregnant mares. This response cannot be induced during early pregnancy, neither with endogenous nor with exogenous oxytocin, thus implicating an important role for this process in MRP in the horse (Starbuck et al., 1998). However, the mechanisms underlying the decreased oxytocin responsiveness in the pregnant mare are controversially discussed (Sharp et al., 1997).

Another mechanism of MRP in mare is Prostaglandin F$_{2\alpha}$ synthesis. When PGF$_{2\alpha}$ was identified as the mediator of luteolysis in the horse (McCcracken et al., 1999; Stout and Allen, 2001), it seemed true that the embryo prevented luteolysis by suppressing the uterine production of prostaglandins. Prostaglandins are synthesized from arachidonic acid, an essential fatty acid stored in the form of membrane phospholipids of the cell (McCracken et al., 2012). Arachidonic acid is released from phospholipids via phospholipase action and converted into the common intermediate, prostaglandin H2 (PGH2) by prostaglandin synthases (Cyclooxygenase) (Smith and Dewitt, 1996). While cyclooxygenase-1, COX-1 is constitutively expressed in most tissues, cyclooxygenase-2, COX-2 expression is inducible. Terminal prostaglandins are subsequently produced by specific prostanooid synthases like prostaglandins E (PGE synthase) and prostaglandins F (PGF synthase), which catalyse the isomerization of PGH2 to PGF$_{2\alpha}$ and PGF$_{2\alpha}$ respectively (Nelson and Cox, 2000; Schuster, 2002; Banu et al., 2003). Particular attention regarding MRP in the mare has been paid to cyclooxygenase-2, as it is a rate limiting enzyme in prostaglandin synthesis. Cyclooxygenase-2 mRNA and protein have been proved to be up-regulated at days 14 and 15 of the oestrous cycle, but not at corresponding days in pregnant mares (Boerboom et al., 2004; Ealy et al., 2010). Moreover, cyclooxygenase-2 mRNA abundance and PGF$_{2\alpha}$ concentrations have been shown to be reduced by conceptus secretions in an equine endometrial explant culture system (Ealy et al., 2010). Therefore, it has been suggested that the conceptus blocks endometrial PGF$_{2\alpha}$ synthesis at least in part by repressing the induction of cyclooxygenase-2 expression during early pregnancy (Atil et al., 2010; de Ruijter-Villani et al., 2015).

Maternal recognition of pregnancy in the pig

In the pig, cyclical luteolysis occurs during late dioestrus in response to a pulsatile release of PGF$_{2\alpha}$ from the endometrium on days 15 and 16 after ovulation (Cencić and LaBonnardière, 2002). PGF$_{2\alpha}$ is subsequently transported to the ovary by a counter current transfer between the uterine venous system and the ovarian artery and via the lymphatic pathways where it exerts its luteolytic effect (Krzymowski et al., 2008).

Oestrogen also plays a role as a pregnancy recognition signal in pig. Pregnancy recognition in pigs is thought to occur between days 11 and 12 after ovulation (Geisert et al., 1982a). During this time, the blastocyst undergoes marked morphological changes and elongates from a spherical to a tubular and filamentous form (Geisert et al., 1982b, Bazer, 1992). The conceptus also begins to secrete substantial amounts of oestrogens which are known to function as the primary pregnancy recognition signal in pigs (Perry et al., 1973; Fischer et al., 1985). These conceptus-derived oestrogens have been implicated in causing a shift in endometrial PGF$_{2\alpha}$ secretion from an endocrine (towards the uterine venous drainage) to an exocrine (towards the uterine lumen) direction (Bazer, 1993b). Luteolytic PGF$_{2\alpha}$ is consequently sequestered within the uterine lumen where it is unavailable to exert its luteolytic effect on the CL (Spencer, 2004). Additionally, the retrograde transfer of PGF$_{2\alpha}$ from the venous blood and uterine lymph into the uterus, and the ability of the uterus vein and artery wall to accumulate PGF$_{2\alpha}$ could also constitute part of the putative mechanism of CL protection during early pregnancy in pigs (Krzymowski et al., 2008). Application of exogenous oestrogens has been shown to induce pseudo-pregnancy in cycling gilts when administered from days 11 to 15 of the oestrous cycle (Geisert et al., 1982a), thus confirming an involvement of oestrogens in MRP in the sow.

Another supportive mechanism by which the conceptus is thought to inhibit luteolysis in the pig is by changing prostaglandin synthesis in favour of luteoprotective Prostaglandin E$_{2}$ (PGE$_{2}$). Indeed, a luteoprotective effect of PGE$_{2}$ has been frequently demonstrated in pigs (Waclawik et al., 2009). It has been suggested that oestrogens (and PGE$_{2}$) produced by the porcine conceptus modulate the expression of key enzymes in PG synthesis in the trophoblast and the endometrium, resulting in a changing pattern of PGF$_{2\alpha}$ and PGE$_{2}$ secretion during early pregnancy (Christens et al., 1994). Indeed, increased mRNA levels of microsomal cyclooxygenase-1 with simultaneous down regulation of prostaglandin F synthase and carbonyl reductase-1 (CBR1), which converts PGE$_{2}$ into PGF$_{2\alpha}$, has been observed in day 10-13 pregnant pigs (Waclawik et al., 2009). This may cause predominance of endometrial PGE$_{2}$ secretion and therefore be an effective agent in increasing the PGE$_{2}$/PGF$_{2\alpha}$-ratio.

Furthermore, Interferons have also been recognized to play a role in MRP in pig. The porcine trophoblast secretes interferons between days 12 and 20 of gestation (La Bonnardiere et al., 1991), for example the major type II interferon (interferon gamma, IFNγ), which is secreted in substantial amounts with a peak of synthesis being observed on days 15-16 of pregnancy and a novel Type I interferon (interferon delta, IFNδ) (Lefevre et al., 1998).
In contrast to the ruminant interferon tau, IFNγ does not appear to exhibit anti-luteolytic properties in the pregnant sow (Lefèvre et al., 1998). However, recent studies support a role for porcine trophoblast interferons in conceptus implantation as they may stimulate the remodeling and/or depolarization of the uterine endometrial epithelium as a prerequisite for blastocyst attachment and establishment of a functional placenta (Cencic et al., 2002; Cencic et al., 2003).

**Maternal recognition of pregnancy in domestic ruminants**

Cyclical luteolysis in domestic ruminants is induced by an oxytocin-dependent pulsatile release of endometrial PGF$_{2\alpha}$ during late diestrus (Sakamoto, 2016). The ongoing exposure to progesterone thereby negatively auto-regulates the expression of the progesterone receptor in the endometrial epithelium, closely followed by increases in epithelial oestrogen receptor (ESR) and oxytocin receptor (OXTR) (Spencer et al., 1995a; Spencer et al., 1995b). This allows oxytocin to induce the uterine release of PGF$_{2\alpha}$ pulses. In ruminants, the posterior pituitary acts as the central oxytocin pulse generator (Bazer, 2013). Moreover, a positive feedback-loop has been described between luteal oxytocin and uterine Prostaglandins (PGs), hence amplifying the luteolytic pulses of PGF$_{2\alpha}$ (Wathes et al., 1995). Due to the unique structure of its vascular utero-ovarian plexus, PGF$_{2\alpha}$ is then transported directly from the uterus to the ovary, possibly by a prostaglandin transporter-mediated mechanism, where it exerts its luteolytic effect (Lee et al., 2010).

Interferon tau (IFNτ), a ruminant-specific member of the type I IFN family, which is synthesized and secreted in substantial amounts by the mononuclear cells of the conceptus trophoderm, is well established as the primary pregnancy recognition signal in ruminants (Roberts et al., 1999; Ford et al., 2012). The expression of IFNτ occurs during a defined period of conceptus development in cattle and sheep (Robinson et al., 2008). IFNτ mRNA and protein are first detected as trophoderm forms at the late morula to early blastocyst stage of development and increase with advancing age of the spherical conceptus (Kubisch et al., 1998). Coincident with the time of MRP, the conceptus changes from a spherical to a tubular and filamentous form and IFNτ secretion increases dramatically at days 14–15 of pregnancy in cattle and at days 12–13 of pregnancy in ovine conceptuses (Ealy and Yang, 2009). IFNτ subsequently acts on the endometrium in a paracrine manner to prevent generation of the luteolytic cascade leading to endometrial secretion of PGF$_{2\alpha}$ (Parent et al., 2002). In pregnant ewes, it has been supposed that IFNτ suppresses transcription of the ESR1 gene and thereby prevents oestrogen to induce expression of the OXTR gene, as it would normally occur during the oestrous cycle (Spencer et al., 2007). In cows, although much of the available data support with this hypothesis in sheep, evidence for a similar mechanism operating is less clear, since OXTR is up-regulated prior to ESR1 expression during the oestrous cycle (Xiao et al., 1999). Therefore, it is implicated that the bovine conceptus probably exerts a rather direct effect on endometrial OXTR gene expression (Robinson et al., 2001).

Apart from the role of IFNτ as pregnancy recognition factor in ruminants, IFNτ is further known to stimulate expression of a number of so-called IFNτ-stimulated genes (ISGs) that are hypothesized to play a role in endometrial differentiation and conceptus implantation (Kim et al., 2003; Wolf et al., 2003; Avan-tika et al., 2015). A systematic study of maternal transcriptome changes in response to the presence of an embryo on day 18 of pregnancy in cattle revealed 87 genes up-regulated in pregnant animals during this time (Forde et al., 2011). Almost one half of these genes were known to be stimulated by type I IFNs (Ott and Gifford, 2010). A functional classification of the identified genes revealed several different biological processes involved in the preparation of the endometrium for the attachment and implantation of the embryo. Such genes are involved in modulation of the maternal immune system and genes relevant for cell adhesion and for remodelling of the endometrium (Klein et al., 2006).

In addition to the afore-mentioned pregnancy recognition signals in ruminants, it seems likely that PGE$_2$, produced by the blastocyst or the endometrium, may also counteract the luteolytic effects of PGF$_{2\alpha}$ in pregnant ruminants. As a stimulator of cAMP and a vasodilator, PGE$_2$ has properties that are opposite to PGF$_{2\alpha}$ (Dorniak et al., 2012). In support of this view, the infusion of PGE$_2$ into the uterus of non-pregnant ewes and cows delay luteolysis (Reynolds et al., 1983). Moreover, an increase of PGE$_2$ in uterine venous blood has been reported during early pregnancy in ewes (Arosh et al., 2004). The structural similarity between prostaglandins namely PGF$_{2\alpha}$, and PGE$_2$ has implications on their bioavailability, site and mode of action in the uterus (Weems et al., 2006). IFNτ has been shown (using cultured bovine endometrial cells) to transform the response of the endometrium to oxytocin from stimulating PGF$_{2\alpha}$ to stimulating PGE$_2$ (Asselin, et al., 1997a, Asselin et al., 1997b). Furthermore, it has also been reported that recombinant bovine IFNτ reduces PGF$_{2\alpha}$ synthesis by blocking the oxytocin-induced expression of COX-2 and prostaglandin F synthase (Xiao et al., 1999). Thus, IFNτ may act via multiple pathways to protect the CL from luteolysis during early gestation in ruminants.

**Maternal Recognition of Pregnancy and Early embryonic mortality**

Infertility and subfertility are major problems in domestic livestock and in humans (Rahman, 2006). The majority of embryonic mortality occurs after fertilization and during the first two to three weeks of pregnancy in animals (Shirazi, 2016). Direct effects of embryonic mortality are reflected in reduced conception rates, reduced litter size and reduced reproductive potential of the herd. The ability of the dam to recognize the conceptus is essential to pregnancy success. Pregnancy loss during the early stage of gestation has been recognized as one of the major causes of infertility in cattle and other ruminants (Diskin and Morris, 2008). This has been attributed partly to failure of the maternal recognition of pregnancy (Dey et al., 2004). Hence, reducing the considerable economic losses associated with poor reproductive performance in livestock requires the simultaneous improvement
in management strategies such as nutrition, health management and the mechanisms involved in maternal recognition of pregnancy.

**Conclusion**

The interaction between the conceptus and the maternal organisms at the conceptus-uterine interphase is essential for the intra-uterine survival of the conceptus. Different mechanisms are employed by various species of animals to maintain the corpus luteum (luteostasis) and sustain the supply of MRP factors. The failure of these mechanisms will lead to early embryonic mortality and subsequently subfertility and or infertility. Understanding of the mechanisms regulating the conceptus development and exploration of the signal transduction systems (through hormones, proteins and cytokines) that permit embryonic implantation and survival within the uterus could facilitate the development of future strategies to ameliorate the early embryonic losses. Perturbations of the MRP by environmental factors such as heat stress, nutritional stress, etc. can lead to early embryonic mortality. With increasing concern worldwide focused on climate change and food security, it is pertinent to explore how these factors affect MRP in domestic animals. This will not only improve reproductive efficiency but also guarantee food security. Therefore, a better understanding of the concept of MRP in animals will enhance managing cases of early embryonic mortality and subfertility (or infertility) and ultimately improved livestock production.

**Conflict of interest**

None declared.

**References**


