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The Paracrinology of Tubal Ectopic Pregnancy

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Abstract

As part of successful human reproduction, the Fallopian tube must provide a suitable environment for pre-implantation development of the embryo and for efficient transport of the embryo to the uterus for implantation. These functions are coordinated by paracrine interactions between tubal epithelial, smooth muscle and immune cells and the cells of the developing embryo. Alterations in these signals can lead to a tubal microenvironment encouraging of embryo implantation and to dysregulated tubal motility, ultimately resulting in inappropriate and early implantation of the embryo in the Fallopian tube. Here, we highlight novel and emerging concepts in tubal physiology and pathobiology, such as the induction of a receptive phenotype within the Fallopian tube, leading to ectopic implantation. *Chlamydia trachomatis* infection is a risk factor for tubal ectopic pregnancy. Activation of toll-like receptor 2 (TLR-2) in the Fallopian tube epithelium, by *C. trachomatis* has recently been demonstrated, leading to the dysregulation of factors involved in implantation and smooth muscle contractility, such as prokineticins (PROK), activin A and interleukin 1 (IL-1). The Fallopian tube has also recently been shown to harbour a unique population of immune cells, compared to the endometrium. In addition, the complement of immune cells in the Fallopian tube has been reported to be altered in Fallopian tube from women with ectopic pregnancy. There are increasing data suggesting that vascularisation of the Fallopian tube, by the embryo during ectopic pregnancy, differs from that initiated in the uterus during normal pregnancy. This too, is likely the result of paracrine signals between the embryo and the tubal microenvironment.

1.1 Introduction

Ectopic pregnancy occurs when an embryo implants outside of the uterus, the majority of which occur in the Fallopian tube (Farquhar, 2005; Shaw et al. 2010a; Sivalingam et al. 2011; Varma and Gupta, 2009). Despite the fact that ectopic pregnancies occur in approximately 1-2% of pregnancies and are a major cause of maternal morbidity and mortality in the first trimester, very little is know about the etiology of this condition (Brown and Horne, 2011; Shaw et al. 2010a; Varma and Gupta, 2009). However, several risk factors for ectopic pregnancy have been identified and include: cigarette smoking, *Chlamydia trachomatis* infection, *Neisseria gonorrhea* infection, previous surgery and in-vitro fertilization (Bouyer et al. 2003; Pisarska et al. 1998; Tay et al. 2000; Varma and Gupta, 2009). Knowledge of the underlying mechanisms leading to tubal ectopic pregnancy has thus far been based largely on in-vitro studies, some of which will be discussed here. Tubal

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ectopic pregnancy rarely occurs in animals (Corpa, 2006), hindering the development of an animal model for studying this condition.

The Fallopian tube plays a crucial role in successful human reproduction. It transports the embryo to the uterus for implantation and supports pre-implantation development of the embryo by providing nourishment and mediating maternal-embryo signals (Croxatto, 2002; Jansen, 1984; Mastroianni, Jr., 1999). Tubal function is controlled by local interactions between different cell types, mediated by paracrine mechanisms. While present in the Fallopian tube, the embryo remains surrounded by the zona pellucida, a glycoprotein membrane which limits direct interactions between the embryo and tubal cells. This further indicates the requirement for paracrine signalling between the embryo and the tubal microenvironment. However the nature of protein-factor diffusion regulation by the zona pellucida is not well understood. In humans, signals between the tubal epithelium and smooth muscle, with additional signals believed to come from the embryo, collectively modulate tubal motility (Croxatto, 2002; Eddy and Pauerstein, 1980; Lyons et al. 2006a; Lyons et al. 2006b). There also exists dialogue between the embryo and tubal epithelial, immune and endothelial cells (Horne et al. 2011; Shaw et al. 2010a; Yoshinaga, 2008). Coordination of various cellular functions through these paracrine signals facilitates the timely embryo-tubal transport and a tubal environment conducive to the support of early embryo development (Croxatto, 2002; Shaw et al. 2010a; Yoshinaga, 2008). The mechanisms controlling the co-ordination of oviductal transport differ between species and in humans, appear to be dependent on the presence of the embryo within the Fallopian tube (Croxatto, 2002). Conditions causing dysregulation of these paracrine signals, such as tubal damage resulting from infection, or cigarette smoking (Bouyer et al. 2003; Pisarska et al. 1998; Tay et al. 2000; Varma and Gupta, 2009) are thought to alter tubal transport and the tubal microenvironment, inducing a receptive phenotype in the Fallopian tube, predisposing to ectopic pregnancy.

Here, we provide descriptions of the different forms of paracrine dialogue taking place within the Fallopian tube which, when dysregulated, may lead to ectopic implantation. Figure 1 is a schematic summary of the various interactions described here.

1.2 Tubal epithelial-smooth muscle interactions

Effective embryo-tubal transport is achieved through a combination of smooth muscle contractility and ciliary beat within the Fallopian tube (Halbert et al. 1976; Lyons et al. 2006b). The latter activity is regulated, largely, by paracrine signals between the tubal secretory and ciliated epithelial cells. Prostaglandins and progesterone are proposed regulators of ciliary beat in the Fallopian tube (Jansen, 1984; Lyons et al. 2006b). Ciliary beat frequency has been shown to increase during the progesterone-dominant mid-luteal phase of the menstrual cycle (Lyons et al. 2006b). The Fallopian tube from women with ectopic pregnancy has been shown to contain less ciliated epithelial cells (Vasquez et al. 1983). Animal studies have demonstrated a reduction in tubal ciliary beat frequency upon cigarette smoke exposure in hamsters (Knoll et al. 1995). A tubal organ-culture based study demonstrated an upregulation of proinflammatory tumour necrosis factor (TNF)-α, following infection of the tubal mucosa with *N. gonorrhea* (McGee et al. 1999). The upregulation of TNF-α was associated with sloughing of ciliated epithelial cells from the tubal mucosa (McGee et al. 1999), suggesting that tubal infection may also have an effect on ciliary activity.

Tubal smooth muscle contractility is believed to be regulated by pacemaker cells called Interstitial Cells of Cajal (ICC) (Popescu et al. 2007). ICC are tiny cells which were first identified in the gastrointestinal tract where they were found to regulate peristalsis (Sanders,

1996). Recently, these cells have also been identified in the Fallopian tube, are reported to be in close contact with tubal epithelial cells (Popescu et al. 2007) and have been demonstrated to express the progesterone receptor (Popescu et al. 2007). Progesterone is believed to play a role in the overall regulation of tubal smooth muscle contractility and it is postulated that ICC mediate progesterone control of tubal contractility through paracrine signals to neighbouring smooth muscle cells. These signals are thought to regulate the electrical activity responsible for the control of smooth muscle activity (Popescu et al. 2007; Wanggren et al. 2006).

Nitric oxide (NO) has been demonstrated to control tubal smooth muscle contractility, inducing relaxation of contractions (Ekerhovd et al. 1997; Ekerhovd and Norstrom, 2004). This regulatory mechanism may also be mediated by tubal ICC. A recent study reported increased nitric oxide synthase (NOS) expression, the enzyme responsible for NO synthesis, in murine oviducts infected with *Chlamydia muridarum* (Dixon et al. 2009). In addition, less ICC were found in *Chlamydia* infected oviducts and spontaneous oviductal contractions were found to be absent in these animals (Dixon et al. 2009). The reductions in ICC numbers were found to correlate with NOS expression levels. The authors propose that chlamydial infection induces an immune response in the mouse oviduct, causing an upregulation in NOS expression by oviductal epithelial cells, signaling either ICC apoptosis or reduced ICC proliferation. NOS expression levels have also been shown to be increased in Fallopian tube from women with serological evidence of past *Chlamydia trachomatis* infection (Refaat et al. 2009). These results suggest that a similar scenario may be present in the human Fallopian tube as in the mouse oviduct and this may help to explain the link between chlamydial infection and an increased risk of ectopic pregnancy (Bouyer). Reduced ICC numbers caused by chlamydial infection may signal diminished smooth muscle contractility, and lead to impaired embryo-tubal transport.

1.3 Embryo-smooth muscle interactions

It has been proposed that the embryo itself my influence its own transport in the Fallopian tube through paracrine signals to tubal smooth muscle cells. In keeping with this hypothesis, human chorionic gonadotrophin (hCG) receptors have been identified in the human Fallopian tube (Lei et al. 1993) and hCG has been reported have a relaxing effect on oviductal smooth muscle contractility in pigs (Gawronska et al. 1999). Platelet activating factor (PAF) is another molecule which has been shown to be expressed by human embryos (O'Neill, 1985) and PAF receptors are reported to be expressed on tubal epithelial cells (Velasquez et al. 2001). In an animal study using hamsters, treatment of the animals with PAF inhibitors caused a significant delay in oviductal transport of embryos but not oocytes (Velasquez et al. 1995). This finding was believed to be the result of interrupted PAF paracrine signaling from the embryo to the oviduct, reducing the induction of smooth muscle contractility. These results suggest that disrupted embryo signalling could also play a role in the development of ectopic pregnancy.

1.4 Tubal epithelial-embryo interactions

It is becoming particularly evident that implantation is an inflammatory event and that pro-inflammatory signals are required for the establishment of a receptive endometrium (Jabbour et al. 2009). Increased levels of pro-inflammatory cytokines, induced by paracrine signaling from the embryo, characterize the endometrium during early implantation (Koga and Mor, 2008; Mor and Koga, 2008; Yoshinaga, 2008) and are believed to signal upregulation of proteins required for embryo receptivity, adhesion and invasion (Evans et al. 2009; Jabbour et al. 2009; Sherwin et al. 2007). In the Fallopian tube, it is a pro-inflammatory phenotype caused by tubal damage from infection and or smoking, which is it believed to cause

upregulation of pro-inflammatory cytokines which induce factors promoting embryo receptivity, adhesion and invasion, leading to ectopic pregnancy. Figure 2 summarizes the epithelial-embryo interactions described below.

One such family of proteins proposed to be responsible for the upregulation of pro-inflammatory cytokines in the Fallopian tube are the prokineticins (PROKs). PROKs are ligands for G-protein coupled receptors, prokineticin receptors (PROKR1 and PROKR2) and recently, we reported associations between tubal prokineticin receptor (PROKR) expression levels and either cigarette smoking or past *C. trachomatis* infection (Shaw et al. 2010b; Shaw et al. 2011b).

We found that PROKR1 expression was significantly higher in Fallopian tube from women who were smokers and had high serum cotinine levels, compared to Fallopian tube from non-smokers (Shaw et al. 2010b). Cotinine is an active metabolite of nicotine and is a biomarker for smoke exposure, widely used for in-vitro studies because of its longer half-life in comparison to nicotine (Benowitz, 1983). Fallopian tube explants and immortalized oviductal epithelial cells (OE-E6/E7) were treated with cotinine, at levels found in the serum of smokers, in-vitro. PROKR1 expression levels were increased in tissue explants and in OE-E6/E7 cells treated with cotinine in-vitro, confirming our in-vivo findings. In addition, we identified expression of nicotinic acetylcholine receptor alpha-7 (nAChRα-7) in the Fallopian tube and demonstrated that cotinine signals through this receptor, resulting in increased tubal PROKR1 expression (Shaw et al. 2010b).

Similarly, we identified a significant increase in PROKR2 mRNA expression in Fallopian tube from women with serological evidence of past *C. trachomatis* infection (Shaw et al. 2011b). In-vitro treatment of Fallopian tube explants and OE-E6/E7 cells with *C. trachomatis* also resulted in increased expression of PROKR2, consistent with the in-vivo findings. Increased PROKR2 expression, resulting from *C. trachomatis* infection in-vitro, occurred quite rapidly (within 8 hours) and was also induced by UV-killed *C. trachomatis* organisms, suggesting involvement of a cell surface pattern recognition receptor. We identified activation of toll-like receptor 2 (TLR2) in the tubal epithelium, with subsequent activation of NFκB, in response to *C. trachomatis* exposure. These findings suggest TLR2 activation and induction of an inflammatory phenotype may be an important early feature of *C. trachomatis* infection of the Fallopian tube. That PROKR2 expression continued to be elevated in Fallopian tube from women with serological evidence of past *C. trachomatis* infection, but with no evidence of acute infection, suggests that TLR2 may also be responsible for the long acting immune responses generated by *C. trachomatis* in the Fallopian tube.

PROKs are known for their angiogenic properties, their control of genes important for implantation and their control of smooth-muscle contractility (Li et al. 2001; Maldonado-Perez et al. 2007). As a specific example, PROKs have been reported to upregulated expression of leukemia inhibitor factor (LIF) in the endometrium (Evans et al. 2008; Evans et al. 2009). LIF has been demonstrated to be essential for successful implantation in mice (Fouladi-Nashta et al. 2005) by mediating interactions between endometrial leukocytes and invading trophoblast (Dimitriadis et al. 2005). In the Fallopian tube, increased LIF expression at the implantation site compared to adjacent sites has been demonstrated (Ji et al. 2009). In addition, increased LIF expression has been demonstrated in chronically inflamed Fallopian tube compared to tube with no evidence of inflammation (Ji et al. 2009). Results from our studies propose that increased tubal PROKR expression, in response to cigarette smoke or *C. trachomatis* exposure, may lead to increased PROK signaling, resulting in upregulation of factors, such as LIF, which signal to the embryo an environment suitable for implantation.

Another protein thought to play a role in altering epithelial-embryo dialogue is activin A. Activin A, a member of the TGF-β family, has been shown to be responsive to TLR2 activation with increased expression in inflammatory conditions (Michel et al. 2003). (Guo and Wang, 2009). Activin A expression has been demonstrated in Fallopian tube epithelial cells (Refaat et al. 2004) and expression has been reported to be increased in Fallopian tube from women with ectopic pregnancy who were also serologically positive for *C. trachomatis* infection (Refaat et al. 2009). These findings suggest that induction of TLR2 signaling, in response to *C. trachomatis* infection, may also lead to increased Activin A expression by tubal epithelial cells. Activin A is believed to also play a role in implantation and has also been reported to control expression of leukemia inhibitory factor (LIF). In-vitro studies have also demonstrated that addition of activin A to villous trophoblast explants promotes their transition to an invasive phenotype (Bearfield et al. 2005), further suggesting a role for activin A in the control of implantation.

Interleukin 1 (IL-1) is a pro-inflammatory cytokine reported to be produced by tubal epithelial cells in response to *C. trachomatis* infection (Hvid et al. 2007). IL-1 signaling has been demonstrated to be important in the regulation of normal embryo implantation, where embryo-produced IL-1 plays a role in mediating the dialogue between the endometrium and implanting blastocyst (Simon et al. 1995). IL-1 is reported to be produced by tubal epithelial cells in response to *C. trachomatis* infection (Hvid et al. 2007), leading to induction of IL-8 expression, a pro-inflammatory cytokine able to recruit neutrophils and cause tissue damage (Hvid et al. 2007; Mukaida et al. 1998). Inhibition of the tubal IL-1 receptor has been demonstrated to block cytokine production and reduce deciliation of tubal epithelial cells, in response to *C. trachomatis* infection (Hvid et al. 2007). These results suggest that altered tubal IL-1 expression, in response to *C. trachomatis* infection may modify the dialogue between the embryo and maternal environment, encouraging receptivity.

Cytokines, such as LIF, responsible for mediating maternal-embryo dialogue, are believed to influence the expression of molecules associated with the tubal epithelium which facilitate the apposition, adhesion and invasive stages of implantation. Such molecules include adhesion molecules and structures including integrins, mucins and pinopodes. Very little is known about the expression of adhesion molecules in the Fallopian tube and in tubal ectopic pregnancy. However, alpha-five and beta-3 integrins, known to be important for embryo adhesion, are reported to be expressed at higher levels in the Fallopian tube during the window of implantation, similar to levels in the endometrium (Lessey et al. 1992). Tubal mucin 1 (MUC1) levels also mirror endometrial expression patterns, increasing during the mid-luteal phase of the menstrual cycle (Al Azemi et al. 2009; Horne et al. 2006; Savaris et al. 2008). Cleavage and removal of MUC1, by embryo-produced factors, is believed to facilitate embryo implantation (Meseguer et al. 1998). Reduced MUC1 expression is reported in Fallopian tube from women with ectopic pregnancy and suggests increased receptivity of the tubal environment.

1.5 Tubal immune cell-embryo interactions

During endometrial implantation, trophoblast invasion is believed to be controlled, at least in part, by large numbers of $CD56^{bright}CD16^{-}$ NK cells, which interact with the trophoblast through specialized receptors (Moffett-King, 2002). These cells infiltrate the endometrium during the mid-secretory phase of the menstrual cycle, under the influence of progesterone (Moffett-King, 2002).

Interestingly, $CD56^{bright}$ have been shown to be absent from the non-pregnant and pregnant Fallopian tube by immunohistochemistry and flow cytometry (Shaw et al. 2011a; Vassiliadou and Bulmer, 1998; von Rango et al. 2001) Absence of these cells in the

Fallopian tube is believed to be the reason for the uncontrolled trophoblast invasion associated with tubal ectopic pregnancy. Recently, a unique population of $CD56^{dim}$ $CD16^{neg}$ cells were identified in non-pregnant Fallopian tube (Shaw et al. 2011a) and in Fallopian tube from women with ectopic pregnancy (Laskarin et al. 2010). In general, the $CD56^{dim}$ population of cells found in peripheral blood have cytotoxic properties (Le Bouteiller and Piccinni, 2008). However, the population of $CD56^{dim}$ cells identified in the Fallopian tube from women with ectopic pregnancy are reported to be non-cytotoxic, likely due to their lack of CD16 expression (Laskarin et al. 2010). These cells do not produce many of the factors believed to be responsible for apoptosis of trophoblast and subsequent control of trophoblast invasion in the endometrium. These results may help to further explain the uncontrolled trophoblast invasion characteristic in ectopic pregnancy.

In contrast to $CD56^{bright}$ NK cells, the Fallopian tube from women with ectopic pregnancy has also been shown to contain significantly higher numbers of many immune cell subtypes, specifically $CD8^{pos}$ lymphocytes, $CD68^{pos}$ macrophages, $CD11c^{pos}$ dendritic cells, compared to non-pregnant Fallopian tube (Shaw et al. 2011a; Ulziibat et al. 2006). These increased numbers of cells may be a reflection of the elevated circulating steroid hormone levels associated with pregnancy or may be present as a result of embryo implantation. We hypothesize that an altered tubal immune cell milieu may also be predisposing to ectopic pregnancy, due to the attenuated production of cytokines and subsequent distorted signals to the embryo.

1.6 Tubal endothelial-embryo interactions causing pathological angiogenesis

A key feature of successful implantation is the establishment of a supportive vascular network. Vascularization depends on the induction of secreted pro-angiogenic growth factors (Torry et al. 2007), which are regulated by a combination of paracrine signalling molecules as well as hypoxia (Demir et al. 2004; Kayisli et al. 2006; Seval et al. 2008; Zygmunt et al. 2003). Intrauterine implantation is associated with activity of the angiogenic factors, vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) (Plaisier et al. 2007; Smith, 2000; Sugino et al. 2002; Torry et al. 2007). These molecules are produced at the implantation site and act on endothelial cells through their receptors flt-1 (VEGFR1) and fkl-1/KDR (VEGFR2) to exert their effects (Plaisier et al. 2007; Sugino et al. 2002; Torry et al. 2007). Reduced VEGF expression and activity is associated with pre-implantation fertility failure (Carmeliet et al. 1996; Ferrara, 1996). PIGF is a member of the VEGF family and commonly signals through the flt-1 receptor (VEGFR1) (Autiero et al. 2003). PIGF and flt1 expression are relatively low in quiescent vasculature, however their expression has been shown to be significantly elevated during vascular morphogenesis, particularly during placentation (Carmeliet et al. 2001). Although PIGF deficiency has been shown to have a negligible effect on normal vascular and embryo development in mice, PlGF expression is notable at the human intrauterine implantation site and is thought to be produced by the trophoblast during the early stages of pregnancy (Carmeliet et al. 2001; Plaisier et al. 2007; Torry et al. 2007). The normal response to intrauterine implantation is a rise in PlGF that can be measured in the maternal serum (Wu et al. 2001).

Angiogenesis also occurs at tubal implantation sites. VEGF and its receptor KDR have been shown to be up-regulated at the tubal implantation site in ectopic pregnancy compared to elsewhere in Fallopian tube (Lam et al. 2004). Tubal VEGF levels have also been demonstrated to correlate with serum hCG levels suggesting that the embryo itself may induce vascularisation (Lam et al. 2004; Torry and Torry, 1997). Tubal ectopic pregnancy can lead to rupture of the Fallopian tube. A recent study found that tubal rupture was more likely to occur in patients with higher serum hCG levels (Goksedef et al. 2011), Given that

hCG levels have been shown to correlate with VEGF levels, it could be that increased hCG levels are associated with increased embryo-induced angiogenesis and vascularization.

Serum VEGF is increased in women with ectopic compared to intrauterine pregnancies(Felemban et al. 2002). The increased VEGF levels observed at tubal implantation sites compared to elsewhere in the Fallopian tube are thought to be induced by hypoxia at the implantation site, therefore resulting in development of an efficient blood supply for the embryo (Ikeda et al. 1995; Shore et al. 1997). In contrast to VEGF, serum PIGF levels have been shown to be reduced in women with ectopic pregnancy compared to women with intrauterine pregnancy (Horne et al. 2011). In addition, trophoblast isolated from tubal implantation sites is reported to express significantly lower levels of PIGF mRNA and protein than trophoblast isolated from intrauterine pregnancies (Horne et al. 2011). It has been proposed that the angiogenesis occurring at the tubal implantation site differs from angiogenesis occurring in the endometrium during intrauterine implantation. Given the reduced expression of PIGF in trophoblast from tubal ectopic pregnancy, the angiogenic differences between tubal and intrauterine implantation sites are thought to be the result of distorted paracrine signals from the embryo due to its exposure to an altered microenvironment in the Fallopian tube, compared to in the endometrium.

1.7 Summary and Conclusions

Fallopian tube function is controlled by local interactions between different cell types, mediated through paracrine mechanisms. Dysregulation of these paracrine mechanisms caused by tubal damage, infection or smoking, are believed to alter local interactions within the tubal environment. These local interactions include dialogue between tubal cells and between tubal cells and the embryo. Here, we have outlined mechanisms by which, collectively, altered paracrine dialogue-mediated communication between the different cell types of the Fallopian tube can lead to impaired tubal motility and to stimulation of a receptive phenotype resulting in tubal ectopic pregnancy.

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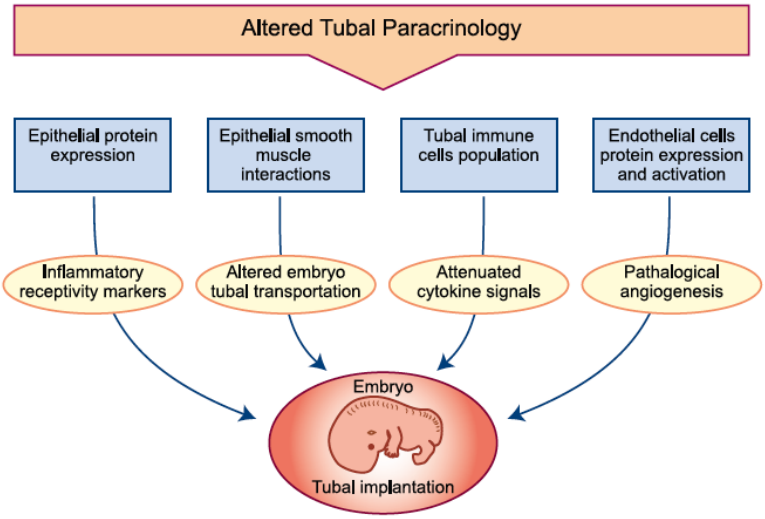

Figure 1.
Summary of the interactions occurring between tubal cells and the embryo within the Fallopian tube and how alterations in these signals lead to tubal implantation

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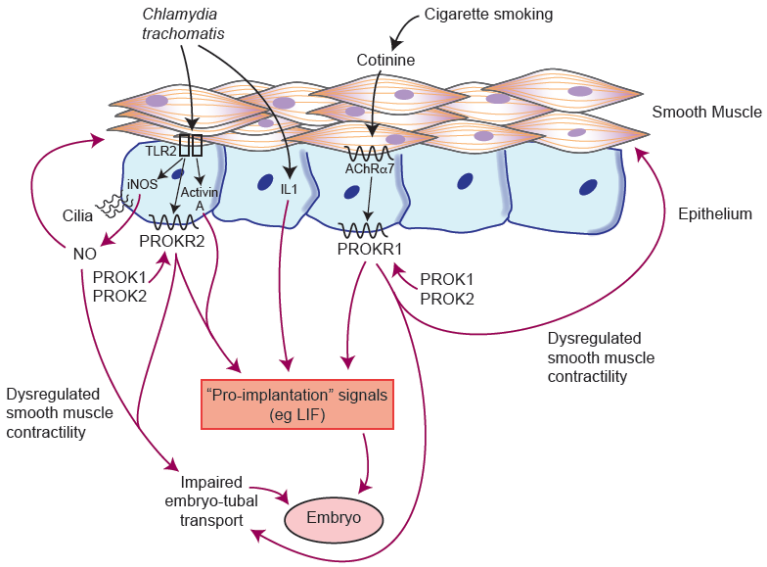

Figure 2.

Schematic representation of the altered paracrine signalling mechanisms within the Fallopian tube and their proposed mechanisms in the development of ectopic pregnancy