

Toll-Like Receptors in the Cycling Female Reproductive Tract and During Pregnancy

Vikki M. Abrahams*

Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, 06520, USA

Abstract: For many years it was thought that the female reproductive tract was a sterile environment, devoid of immune cells or pathogens. We now know that the immune system represents an important component of reproductive tissues, influencing many of its biological functions. Similarly, bacteria are present within the female reproductive tract as a normal component. Therefore, the female reproductive tract must promote a certain level of host protection against pathogens whilst maintaining commensal flora, in addition to facilitating normal menstrual cycling, successful fertilization and implantation. Furthermore, during pregnancy, the human endometrium becomes an immunologically unique site that again, must maintain host defense against an array of microbial pathogens, but must also sustain the semi-allogeneic fetus and placenta. In addition to the cells of the immune system, the mucosal epithelium of the female reproductive tract, as well as tissues of the maternal-fetal interface, may actively participate in the control of pathogens, however, the precise mechanisms by which this occurs are poorly understood. Toll-like receptors (TLR) are key components of the innate immune system which recognize conserved sequences on the surface of microorganisms and trigger effector cell functions. We and others have shown the expression of Toll-like receptors in epithelial cells of female reproductive tissues and at the maternal-fetal interface, suggesting that these specialized cells can recognize and respond to the presence of microorganisms and coordinate an immune response. Clinical studies have shown a strong association between intrauterine infections and fertility problems as well as certain pregnancy complications. Therefore, innate immune responses within the female reproductive tract against microorganisms may have a significant impact on implantation and on the success of a pregnancy. This review will discuss the role of Toll-like receptors in the normal cycling female reproductive tract and at the maternal-fetal interface during pregnancy.

Keywords: Infection, Innate immunity, Mucosal epithelium, Placenta, TLR.

INTRODUCTION

The female reproductive tract is a complex mucosal system that must be able to tolerate the presence of spermatozoa in order to promote successful fertilization, and to allow implantation of a semi-allogeneic fetus, all the while maintaining host defense against potential pathogens. For many years the female reproductive tract was viewed as a sterile environment, devoid of microbes or immune cells [1]. We now know that the immune system represents an important component of the reproductive tract [2,3], influencing many of its biological functions [4,5]. Furthermore, the lower tract is populated by commensal microorganisms, which at times, can become exposed to the upper tract. It is, therefore, the mucosal epithelium of the reproductive tract that provides this specialized organ with the first barrier of defense and is equipped to respond to pathogens, whilst sustaining commensal microorganisms. One mechanism by which this occurs is through the innate immune system's process of pattern recognition [6]. Toll-like receptors are a family of pattern recognition receptors that mediate this function by recognizing conserved sequences on the surface of microorganisms and triggering effector cell functions [7].

Recent studies have demonstrated the expression of Toll-like receptors throughout the cycling female reproductive tract, as well as at the maternal-fetal interface during pregnancy, suggesting that these sites may be able to detect and respond to pathogens. This review will discuss the advances in the field of Toll-like receptor expression and function within the pregnant and non-pregnant female reproductive tract.

MICROBIOLOGY OF THE FEMALE REPRODUCTIVE TRACT

Tissues of the lower reproductive tract are populated by a rich commensal microflora which limit the growth of more virulent microorganisms [8]. The major commensals at this site include *Lactobacillus*, *Gardnerella vaginalis* and *Escherichia coli* [9]. In addition, common pathogens that may populate the lower genital tract include *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Candida albicans* [8,9]. The mucus produced by the cervix provides somewhat of a barrier, however, this can be breached and the upper tract is, on occasion, exposed to both commensal bacteria and pathogenic microbes through either peristaltic contractions or intercourse [10,11]. Infection within the upper tract can have serious consequences, such as chronic pelvic inflammation, infertility and pregnancy complications [12-14]. Therefore, such infectious agents must be quickly removed, whilst sustaining the resident microbial population of the lower tract.

*Address correspondence to this author at the Department of Obstetrics, Gynecology and Reproductive Sciences, Reproductive Immunology Unit, Yale University, School of Medicine, 333 Cedar Street, FMB 301, New Haven, CT 06520, USA; Tel: 203 737 1405; Fax: 203 785 4883; E-mail: vikki.abrahams@yale.edu

INFECTIONS DURING PREGNANCY

Clinical studies have shown a strong association between certain pregnancy complications and intrauterine infections [13,15], suggesting that innate immune responses to pathogens may affect the outcome of a pregnancy. Preeclampsia and intrauterine growth restriction (IUGR) are both thought to be associated with infection [16-18] and a link between preterm labor and intrauterine infections is now well established. Indeed, infections have been reported to be responsible for up to 40% of preterm labor cases [19]. Furthermore, 80% of preterm deliveries occurring at less than 30 weeks of gestation have evidence of infection, suggesting that an intrauterine infection may occur early in pregnancy, preceding such pregnancy complications [13,15]. Common infections associated with preterm labor where membranes remain intact include *Ureaplasma urealyticum*, *Mycoplasma hominis* and *Gardnerella vaginalis*, however, no one particular microorganism has been attributed a causative role. While an infection may enter the uterus from either the abdominal cavity via the fallopian tubes or inadvertently during procedures such as amniocentesis, most intrauterine infections in cases of preterm labor, are normally found in the vagina. Therefore, it appears that the primary route for a microorganism is to ascend to the uterus from the lower tract [13,20]. Once there, the microbe might become trapped, and if not quickly cleared, may breach the fetal membranes to infect the fetus, or may enter the tissues of the maternal-fetal interface. Infection, therefore, represents an important and frequent mechanism of disease, yet, the precise molecular mechanisms by which infection can affect a pregnancy remain undefined.

ROLE OF TOLL-LIKE RECEPTORS IN INNATE IMMUNE RESPONSES

The innate immune system represents the immunological first line of defense against invading pathogens through its ability to distinguish between what is non-infectious self and infectious non-self [7]. One way in which the innate immune system achieves this is through an evolutionary conserved system of pattern recognition [6]. Cells of the innate immune system express a family of receptors known as Toll-like receptors (TLR) which recognize and bind to highly conserved sequences known as pathogen-associated molecular patterns (PAMPs). Pathogen-associated molecular patterns are unique to, and expressed by microorganisms. The ligation of Toll-like receptors by PAMPs results in an inflammatory response generated against the invading pathogen [21].

The *Toll* gene was originally discovered in *Drosophila* [22,23] and was found to be responsible for anti-fungal and anti-bacterial properties in the adult fly [24,25]. To date, 11 mammalian *Toll* homologues have been identified, 10 of which are known to be expressed by humans (TLR-1 - 10) [26]. Ligation of TLR by microbial products results in an inflammatory immune response characterized by the production of cytokines and anti-microbial factors. Furthermore, through the regulation of co-stimulatory molecules, TLR may also facilitate the development of adaptive immune responses [21]. Toll-like receptors are transmembrane proteins which have an extracellular domain containing leucine-rich repeat motifs. Each receptor differs

in its ligand specificity. So while individually, TLR respond to limited ligands, collectively the family of TLR can respond to a wide range of proteins associated with bacteria, viruses, fungi and parasites. TLR-4, the first human Toll-like receptor to be identified, is the specific receptor for responses to gram-negative bacterial lipopolysaccharide (LPS) [27,28]. In addition, TLR-4-mediated responses may require additional molecules, such as CD14 or MD-2 [29,30]. TLR-2 has the widest specificity of the TLRs since it can recognize gram-positive, gram-negative and mycobacterial associated lipoproteins, gram-positive peptidoglycan and lipoteichoic acid and fungal zymosan [31-36]. TLR-2 recognition of some microbial products also appears to be dependent upon the formation of heterodimers with either TLR-1 or TLR-6 [37,38]. TLR-3 binds to viral dsRNA, TLR-5 binds bacterial flagellin, TLR-8 recognizes ssRNA and TLR-9 binds bacterial CpG DNA [39-41]. The natural ligands for human TLR-7 and TLR-10 are, as yet, undetermined.

TOLL-LIKE RECEPTOR SIGNALING

While extracellularly, each TLR is distinct in its specificity receptors may signal through a common pathway. Toll-like receptors have an intracellular domain which is highly homologous to the type-1 Interleukin-1 receptor (IL-1R) and is known as the Toll/IL-1R homology region (TIR) [42]. Both TLR and the IL-1R recruit and interact with the adapter signaling protein, myeloid differentiation factor 88 (MyD88) [43]. Following ligation of a TLR by its ligand, MyD88 becomes associated with the intracellular domain of the receptor through a TIR-TIR interaction [44,45]. In turn, MyD88 through its death domain (DD) recruits and activates the DD-containing serine/threonine kinase, IL-1R associated kinase (IRAK) [44]. IRAK then dissociates from the receptor complex and becomes associated with TRAF-6 [46]. Downstream activation of the NF- κ B and MAP kinase signaling pathways then occurs, resulting in the production of pro-inflammatory cytokines, anti-inflammatory cytokines, chemokines, and anti-microbial peptides, such as defensins [47,48]. Toll-like receptors-3 and -4 can also signal *via* MyD88-independent pathways, resulting in the production of type I interferons (IFN α and IFN β) [26].

TOLL-LIKE RECEPTORS IN THE NON-PREGNANT REPRODUCTIVE TRACT

Toll-like receptors are widely expressed throughout the immune system, particularly the innate. However, Toll-like receptors can also be expressed by non-immune cells, especially in those that constitute part of a biological barrier, such as the mucosal epithelium. Indeed, the expression of Toll-like receptor in mucosal systems is thought to be important for host defense against external pathogens [49,50]. While many studies of mucosal tissues have focused on the intestinal and respiratory tracts, there is growing evidence that the mucosa of reproductive organs is an important immunological barrier. Therefore, the expression of Toll-like receptors within the female reproductive tract may provide this system with a specialized mechanism of host defense [51].

The expression of Toll-like receptors has been detected throughout the female reproductive tract. Pioli *et al.* [52]

have reported the expression of TLR-1 - TLR-6, as well as the accessory proteins, MyD88, MD-2 and CD14 in tissues of both the upper and lower tracts. Interestingly, TLR-2 and TLR-4 expression levels significantly vary between the sites of the genital tract. This is likely to reflect the varying populations and distributions of immune cells within these tissues [3], however, to date, there are no studies that have characterized immune cell expression of TLR within the human reproductive organ. Nonetheless, while immune cells constitute a significant cellular component of mucosal sites, it is the epithelial cells that first become exposed to pathogens and can initiate immunological responses through the secretion of antibodies, cytokines and anti-microbial factors [8,53]. In support of this, primary endometrial epithelial cells have been shown to express TLR-1 - TLR-6, and TLR-9 [54]. Furthermore, TLR-3 expression levels by endometrial epithelial cells change with the menstrual cycle, increasing in the secretory phase, suggesting that TLR-3 expression and, therefore, local responses to a viral infection may be under hormonal control [55]. The expression profiles of Toll-like receptors by cervical and vaginal epithelium mirror each other, but differ from endometrial epithelial cells. Fichorova *et al.*, [56] have shown that primary endocervical cells express TLR-1, TLR-2, TLR-3 and TLR-6, but not TLR-5, TLR-4 or its accessory molecule MD-2, suggesting that responses to bacterial LPS and flagellin are unachievable within the lower genital tract. Such unresponsiveness to LPS may explain how gram-negative bacteria are able to populate the lower tract [9]. Moreover, the expression of other Toll-like receptor family members grant the mucosal epithelium of the female reproductive tract the potential to recognize microorganisms in a site specific manner.

TOLL-LIKE RECEPTOR FUNCTION IN THE REPRODUCTIVE TRACT

As discussed above, the epithelial cells of the female reproductive tract can mount immunological responses and Toll-like receptors may provide such innate mechanisms. However, in some cases innate immune functions may exacerbate certain pathological conditions. One example is where entry of the gram-negative bacteria *Chlamydia trachomatis* into the upper female reproductive tract can lead to chronic inflammation of the fallopian tubes, possibly resulting in infertility, ectopic pregnancy or pregnancy loss [14]. Studies using TLR-2 and TLR-4 knockout mice have shown, while both TLR-2 and TLR-4 may play a role in the resolution of such an infection through the production of inflammatory mediators, TLR-2 may also responsible for promoting the oviduct pathology that is associated with this infection [57]. While this study highlights the detrimental effects of innate immune responses when not adequately controlled, it also supports a functional capacity for Toll-like receptors within the female reproductive tract.

Recent *in vitro* studies have begun to examine the precise function of Toll-like receptors in the female reproductive tract epithelia. Primary endocervical cells, expressing TLR-1, TLR-2, TLR-3 and TLR-6 are capable of responding to PAMPs expressed by *Neisseria gonorrhoeae* to produce pro-inflammatory cytokines [56,58]. Functional studies on endometrial epithelial cells have utilized cell lines and while

these were derived from adenocarcinomas [59,60], they can provide a useful *in vitro* model for studying cellular functions. However, some inconsistencies have been raised in TLR responses. The ECC-1 cell line expresses TLR-1 - TLR-9, but only secretes cytokines and chemokines in response to TLR-2, TLR-4 and TLR-5 ligands [61]. In contrast, the uterine epithelial cell line, RL95-2, which also expresses TLR-3, has been shown to secrete IL-8 in response to its agonist, poly(1:C) [54]. Furthermore, both ECC-1 and Ishikawa cells express TLR-4 but only ECC-1 cells appear to respond to LPS [54,61]. These findings suggest that TLR responses may be selective to particular ligands in certain cell lines. Alternatively, a lack of TLR response may arise from the TLR cellular localization. Immunocytochemical studies of epithelial cells have shown high levels of TLR expressed intracellularly with no cell surface expression [62]. Therefore, further immunocytochemical studies with these cell lines are required to determine if this is the case. Notwithstanding, the production of chemokines, such as IL-8 and MCP-1, in response to TLR ligation suggests that endometrial epithelial cells have the capacity to recruit leucocytes for the induction of an immune response, should a bacteria breach the epithelial barrier. Together, these studies suggest that Toll-like receptors play an important role in host defense within the normal cycling female reproductive tract. However, the epithelial cells of the female reproductive tract are not only exposed to pathogens, but also commensal organisms and this raises a paradox.

TOLL-LIKE RECEPTOR RESPONSES TO COMMENSAL AND PATHOGENIC MICROBES

Commensal and pathogenic microorganisms share PAMPs which are recognized by pattern recognition receptors, such as Toll-like receptors. Therefore, commensal and pathogenic microbes should have the same ability to trigger innate immune responses. This creates the possibility of either hyper-responsiveness to resident microorganisms or the depletion of commensal populations. Yet mucosal systems, including the female reproductive tract, are colonized by commensal microflora, and these systems are not subject to constant inflammation under normal conditions. However, in the presence of a pathogen, a robust immune response can be generated and the infection is resolved. This then raises the question of how a mucosal system, such as the female reproductive tract, can distinguish between what is pathogenic and what is not. The main hypothesis for how this transpires is borne from the *in vitro* and *in vivo* observations of endotoxin tolerance, in which exposure to LPS can result in a temporary unresponsiveness towards a second exposure (reviewed in [63]). Thus, commensal microbes within the FRT may induce tolerance as a result of repeated TLR signaling. Indeed, *in vitro*, TLR-2 and TLR-4 signaling in epithelial cells initially occurs. However, upon a second or a prolonged exposure to PAMPs, signaling fails [64]. There are a number of suggested mechanisms as to how such tolerance might arise. One proposal is based upon the concept that a pathogen is characterized as a microorganism that breaches certain physical barriers, such as a mucosal epithelium [7]. In support of this, studies of the intestinal tract have shown these epithelial cells to express TLR-5, but only on their basolateral side [65]. Therefore, these cells will only respond

to a bacterium that has invaded the basolateral compartment from the apical side. Simply a lack of TLR expression may also account for endotoxin tolerance. As already discussed, TLR-4 is not expressed by cervical or vaginal epithelial cells [56], consistent with observations that following LPS exposure, TLR-4 expression is downregulated [66]. Alternatively, the upregulation of inhibitors of TLR signaling such as Tollip, IRAK-M or SOCS-1 may account for epithelial PAMP tolerance [67,68]. However, once the epithelium is breached, immune cells present within the tissue may quickly respond. These studies suggest that the differential expression of Toll-like receptors in the female reproductive tract may be distributed in such a way as to maintain commensal populations. Further cellular localization studies are greatly needed.

In spite of these findings, a counter argument has recently been proposed (reviewed in [69]). Rather than the immune system attempting to avoid a response towards commensals, it has been suggested that these microbes may in fact be essential for protecting mucosal epithelia from direct tissue injury. Rackoff-Nahoum *et al.* have demonstrated that gut epithelial cells, in a TLR-dependent manner, are constitutively secreting tissue protective factors such as TNF, IL-6, KC-1 and heat shock proteins in response to commensal microbes. Following epithelial damage, as might occur in the presence of an invasive pathogen, commensal-derived ligands may further induce production of these factors in order to limit tissue damage [70]. Other studies also support the role of commensals in promoting the production of cytoprotective factors [71]. These recent findings shed new light on the function of Toll-like receptors and the role of commensal microorganisms in mucosal immunity.

THE ROLE OF TOLL-LIKE RECEPTORS DURING PREGNANCY

As discussed previously, bacterial infections, if present within the uterus during pregnancy, can represent a significant threat to the well-being of the fetus. Indeed, animal models of pregnancy complications have been generated by the administration of gram-negative bacterial LPS [72-76] and Toll-like receptors have been implicated in the pathogenesis of infection-associated prematurity [77,78]. Once present within the uterus, an infectious agent may take one of two main routes, although these are not mutually exclusive. Firstly, an infectious agent may cross the fetal membranes and if successful, proceed to infect the fetus. Alternatively, it may gain access to the maternal-fetal interface by infecting the placenta or maternal decidua [13,15]. Recent findings, by ourselves and others, suggest that certain tissues associated with pregnancy may be able to function as components of the innate immune system by recognizing and responding to bacterial components through Toll-like receptors. However, as will also be discussed such innate immune functions may also contribute to certain pregnancy complications.

Toll-Like Receptor Expression in Fetal Membranes

Invasion of the fetal membranes and amniotic cavity by an infectious agent is characterized by chorioamnionitis and is a major cause of preterm labor [15]. Infection of the

amniotic cavity has been associated with high levels of pro-inflammatory cytokines, such as IL-6 and TNF (reviewed in [79]) and chemokines [80,81] within the amniotic fluid. Indeed, the chorioamniotic fetal membranes have been shown to respond to bacterial components [82,83] and to produce anti-microbial peptides [84]. We now know that amniotic epithelial cells possess the mechanisms necessary to specifically recognize and respond to bacteria. Both TLR-2 and TLR-4 are expressed by amniotic epithelial cells and TLR-2 expression is limited to the basolateral side of these cells [85]. This expression pattern is analogous to previous findings in gut epithelium, supporting the hypothesis that a pathogen must breach certain barriers before a response can be mounted [65]. Interestingly in cases of inflammation, such as in chorioamnionitis, this polarized distribution is lost and TLR-2 and TLR-4 expression becomes upregulated [85]. Moreover, if an infection successfully proceeds to access fetal Toll-like receptors, a severe fetal-inflammatory response may also result contribute to the initiation of preterm labor [86].

Decidual Toll-Like Receptor Expression

Within the decidua there are many immune cells that have the potential to mount an immune response against a pathogen [5]. However, at present we know very little about Toll-like receptor expression within the decidua. Nevertheless, TLR-2 and TLR-4 protein has been detected in term decidua inflammatory immune cells, most likely macrophages and neutrophils [85]. Term decidua cells also express these innate immune receptors, suggesting that decidua stromal cells can contribute to the resolution of an invasive infection [85,87]. In addition we find that first trimester decidua cells express TLR-1, -2 and -4 (Aldo, unpublished data) and studies are currently underway to further characterize the expression and function of decidua TLR.

Toll-Like Receptor Expression in the Placenta

Most Toll-like receptor research in the context of pregnancy has focused on the placenta, although studies are still limited. Normal term placental tissue has been shown to express TLR-1-10 at the mRNA level [88,89]. At the protein level TLR-2 and TLR-4 are expressed in term placenta [90,91]. Holmlund *et al.* demonstrated that term syncytiotrophoblast and intermediate trophoblast cells express TLR-2 and TLR-4 [90]. In contrast, Kumazaki *et al.* found the TLR-4 positive placental cells to be term extravillous and intermediate trophoblasts [91] and such contradictory findings might be a result of the type of antibodies used.

In our studies we have evaluated the expression Toll-like receptors by first trimester trophoblast cells. At the mRNA level we observe expression of TLR-1 - TLR-4 and the TLR inhibitor Tollip, while TLR-6 is not expressed ([92]; Abrahams *et al.*, manuscript in preparation). We have also observed that in first trimester placental tissues, TLR-2 and TLR-4 proteins are highly expressed. Interestingly, the first trimester trophoblast cell populations expressing these receptors are the villous cytotrophoblast and extravillous trophoblast cells. First trimester syncytiotrophoblast cells do not express these TLR and this suggests that the placenta, similar to the chorioamnion, serves as a highly specialized

barrier, protecting the developing fetus against infection [92]. A microorganism will only be a threat to the placenta if the TLR-negative syncytiotrophoblast cell layer is breached and the pathogen has entered either the decidual or the placental villous compartments. Once an infection has gained access to the TLR positive trophoblast cells, a response may be mounted. As described below, the type of pathogen and, therefore, the specific receptor activated may have a significant impact on the type of response generated by the cells of the placenta. What these findings suggest is, like the mucosal epithelial barrier of the female reproductive tract, the placenta may interact specifically with pathogens present at the implantation site and may be able to initiate an immune response.

THE FUNCTION OF TOLL-LIKE RECEPTORS AT THE MATERNAL-FETAL INTERFACE

The apparent expression of Toll-like receptors at the maternal-fetal interface suggests that during pregnancy both maternal and fetally-derived tissues have the potential to recognize and respond to pathogens. Furthermore, the restricted TLR expression patterns in both the placenta and amnion suggest that these tissues provide a specialized immunological barrier which, only if breached, may mount an innate immune response. While it is known that microbial invasion of the chorioamnion results in an inflammatory response from the fetal membranes, *in vitro* studies are still necessary to directly link amniotic Toll-like receptors with such immune function. In contrast, more is known about the function of Toll-like receptors within the placenta. Treatment of term trophoblast cells with LPS has also been shown to induce the production of nitric oxide, which has potent antimicrobial properties, and also MMP-2 [93]. Trophoblast cells from term placental explants can also produce the pro-inflammatory cytokines, IL-6 and IL-8, following Toll-like receptor ligation by microbial components [90]. Studies on first trimester trophoblast cells have shown that treatment with LPS induces the production of G-CSF and RANTES [94]. Since an intrauterine infection may precede implantation, recent work from our laboratory has focused on the function of Toll-like receptors in the placenta during the first trimester of pregnancy. We have found that activation of TLR-4 by LPS triggers first trimester villous cytotrophoblast and extravillous trophoblast cells to generate a classical TLR response, characterized by the increased production of both pro- and anti-inflammatory cytokines [92]. In contrast we find that ligation of TLR-2 by peptidoglycan fails to upregulate cytokine production by trophoblast cells. Instead, activation of TLR-2 induces first trimester trophoblast cells to undergo apoptosis [92]. TLR-2 is thought to require the cooperation of either TLR-1 or TLR-6 for ligand recognition [37,38]. Since first trimester trophoblast cells lack TLR-6, TLR-2 apoptosis may occur as a result of either TLR-2 homodimerization or TLR-1 and TLR-2 heterodimer formation.

Disturbances in the regulation of apoptosis within the placenta appears to be associated with abnormal pregnancy outcome [95]. Elevated trophoblast apoptosis is seen during in pregnancies complicated with IUGR, preeclampsia and in preterm births [96-100]. These complications have also been associated with intrauterine infections [15-18,79]. Therefore,

we hypothesize that Toll-like receptors expressed at the maternal-fetal interface may play an important role in the mechanism of pathogenesis. We predict that certain intrauterine infections during pregnancy may have either a direct or indirect effect upon trophoblast cell survival, depending upon which TLR is activated. A pathogen may directly promote trophoblast cell death through TLR-2. Alternatively, a gram-negative bacteria, through TLR-4, may trigger first trimester trophoblast cells to produce high levels of cytokines, including TNF and IFN , which in turn may promote trophoblast cell apoptosis [101-105]. Together, these studies suggest that trophoblast cells can indeed function similarly to cells of the innate immune system, by recognizing and responding to components of microorganisms and in cases of chronic ligand exposure may promote tissue dysfunction resulting in a complicated pregnancy.

TOLL-LIKE RECEPTORS AS A CLINICAL MARKER

As discussed above Toll-like receptors may play a role in the pathogenesis of certain pregnancy complications such as preterm labor, preeclampsia or IUGR. If this is the case then these receptors may be used as clinical biomarkers of disease. Recently, soluble TLR-2 has been identified [106]. This protein may function by modulating specific TLR-mediated responses. Alternatively, soluble forms of TLR may bind to microorganisms and flag them for destruction by the complement system or by phagocytosis [7]. Soluble Toll-like receptors may, therefore, provide new markers of pregnancy complications as well as a potential target for therapeutic interventions. Alternatively, a genetic approach may provide important information regarding an individual's susceptibility to developing infection-based fertility problems or pregnancy complications. Polymorphisms in several TLR have been identified and have been linked with altered responsiveness [107-109]). Genetic mutations such as these may, therefore, have an impact clinically [110].

SUMMARY

The presence of immune system within the female reproductive tract is increasingly being recognized as an important element for maintaining host protection and promoting reproductive functions. This has been strengthened by the recent findings that Toll-like receptors, a critical component of the innate immune system, are expressed and functional within the genital tract. Through the expression of Toll-like receptors, the mucosal epithelium of the female reproductive tract may function as a component of the innate immune system by promoting direct responses against invading pathogens and by coordinating an inflammatory immune response through the recruitment of immune cells. Similarly, the tissues of the maternal-fetal interface may also recognize and respond to pathogens through Toll-like receptors. However, as with all innate immune processes, inappropriate activation or chronic inflammation can lead to tissue injury. Within the reproductive tract such uncontrolled responses can have severe consequences in terms of fertility or pregnancy complications. While much research is still required, the studies thus far of Toll-like receptors have shed new light on the role of the innate immune system within the reproductive organs of both pregnant and non-pregnant females.

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