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Inflammation and pregnancy: the role of the immune system at the implantation site

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Abstract

The concept that pregnancy is associated with immune suppression has created a myth of pregnancy as a state of immunological weakness and, therefore, of increased susceptibility to infectious diseases. A challenging question is whether the maternal immune system is a friend or a foe of pregnancy. In this review, we discuss data associated to the role of the immune system during pregnancy. We propose a new paradigm in terms of the fetal-maternal immune interaction as well as the immunological response of the mother to micro-organism. Our challenge is to better understand the immunology of pregnancy in order to deliver the appropriate treatment to patients with pregnancy complications as well as to determine public policies for the protection of pregnant women during pandemics.

Keywords

inflammation; pregnancy; TH1/TH2; macrophages; dendritic cells

The idea that pregnancy is associated with immune suppression has created a myth of pregnancy as a state of immunological weakness and, therefore, of increased susceptibility to infectious diseases. A challenging question is whether the maternal immune system is a friend or a foe of pregnancy. In order to discuss this question we will first review some fundamental concepts associated with the immune system and pregnancy.

A fundamental feature of the immune system is to protect the host from pathogens. This function depends upon the innate immune system's capacity to coordinate cell migration for surveillance and to recognize and respond to invading microorganisms. During normal pregnancy, the human decidua contains a high number of immune cells, such as macrophages, natural killer (NK) cells and, regulatory T cells (Treg) [1–3][2,4,5]. B cells are absent from the adaptive immune system, but T lymphocytes constitute about 3–10% of the decidual immune cells [6]. During the first trimester, NK cells, dendritic cells, and macrophages infiltrate the decidua and accumulate around the invading trophoblast cells [7,8]. Interestingly, depletion of immune cells, instead of helping the pregnancy, terminates the pregnancy. Thus, deletion of macrophages, NK cells, or dendritic cells (DC) has deleterious effects on placental development, implantation, or decidual formation [9–14]. In elegant studies, it has been shown that in the absence of NK cells, trophoblast cells are not able to reach the endometrial vascularity leading to termination of the pregnancy [12]. These studies suggest that uNK cells are critical for trophoblast invasion in the uterus. Similarly, depletion of DCs prevented blastocyst implantation and decidual formation [15]. Indeed, this

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study suggests that uDC are necessary for decidual formation and may affect the angiogenic response by inhibiting blood vessel maturation[15].

More recently, Collins *et al*. demonstrate that uDC association, with T cell responses to the fetal "allograft," starkly contrast with their prominent role in organ transplant rejection [16]. All of these data further support the idea that the fetal-maternal immune interaction is more complex than the comparison to transplant allografts [17].

Consequently, the presence of immune cells at the implantation site is not associated with a response to the "foreign" fetus but is attracted to facilitate and protect the pregnancy. Therefore, the immune system at the implantation site is not suppressed—on the contrary it is active, functional, and is carefully controlled.

Is the systemic immunity of the mother suppressed? Although we can find numerous studies describing factors inducing immune suppression (including progesterone, defined as the natural immune suppressor)[18], medical and evolutionary aspects are against the concept of immune suppression. Pregnancy represents the most important period for the conservation of the species; therefore, it is fundamental to strengthen all the means to protect the mother and the offspring. The immune system is one of the most important systems protecting the mother against the environment and preventing damage to the fetus. It is during pregnancy when the maternal immune system is characterized by a reinforced network of recognition, communication, trafficking, and repair; it is able to raise the alarm, if necessary, in order to maintain the well-being of the mother and the fetus. On the other side is the fetus that, without any doubt, provides a developing active immune system that will modify the way the mother responds to the environment, providing the uniqueness of the immune system during pregnancy. Therefore, it is appropriate to refer to pregnancy as a unique immune condition that is modulated but not suppressed [19,20].

This unique behavior explains why pregnant women respond differently to the presence of microorganisms or its products (see Ref. 19 and below). Therefore, pregnancy should not imply more susceptibility to infectious diseases, instead it is a time of life where there is a modulation of the immune system, which leads to differential responses depending not only on the microorganisms but on the stages of the pregnancy.

The allograft paradigm: transplantation versus implantation

Over fifty years ago, Sir Peter Medawar proposed the paradigm of why the fetus, as a semi-allograft, is not rejected by the maternal immune system [21,22]; the presence of the maternal immune system at the implantation site was used as evidence to support this [23]. As a result, investigators pursued the mechanisms by which the fetus might escape maternal immune surveillance and varied hypotheses have been proposed [24]. Medawar's observation was based on the assumption that the placenta is an allograft expressing paternal proteins and, therefore, under normal immunological conditions, should be rejected. However, as our knowledge of placental biology has significantly increased over the last 50 years, we can appreciate that the placenta is more than a transplanted organ. Based on the data discussed here and elsewhere, we suggest that, while there may be an active mechanism preventing a maternal immune response against paternal antigens [25–27], the trophoblast and the maternal immune system have evolved and established a cooperative status, helping each other for the success of the pregnancy [28,29]. We propose that the differentiation and function of immune cells infiltrating the implantation site depends, largely, on the microenvironment created by the placenta. We hypothesize that trophoblast cells can induce the differentiation of immune cells into a trophoblast-supporting phenotype. This hypothesis is supported by our findings that conditioned media from trophoblast cells is able to induce monocyte-like THP-1 cells to secrete cytokines such as IL-6, IL-8, MCP-1, and GRO-α

which has beneficial effects on trophoblast development and function. This trophoblast-immune interaction involves three stages: 1), attraction: trophoblast cells secrete chemokines that can recruit immune cells to the implantation site [10,30]; 2) education: trophoblast cells produce regulatory cytokines that modulate the differentiation process of immune cells[31]; and 3) response: immune cells educated by trophoblast cells respond to signals of the local microenvironment in an unique way [32] (Fig. 1).

Using *in vitro* models for trophoblast immune interaction we have described the characteristics of each of these stages. An example of this interaction is shown in Figure 2 where villi-like structures established in a three-dimensional *in vitro* system are capable of attracting monocytes/macrophages and recruiting them around the trophoblast-derived structures. These macrophages provide support for the culture and enhance trophoblast survival. In the absence of the signals originated from the trophoblast, macrophages remain on the surface and will not migrate through the matrigel [33] (Fig. 2)

The cytokine profile during pregnancy

The definition of pregnancy as a “Th-2” or anti-inflammatory state was enthusiastically embraced and numerous studies attempted to prove and support this hypothesis. This theory postulates that pregnancy is an anti-inflammatory condition [34–36] and a shift in the type of cytokines produced would lead to abortion or pregnancy complications. While many studies confirmed this hypothesis, a similar number of studies argued against this notion [23,37]. The reason for these contradictory results may be due to oversimplification of disparate observations made during pregnancy. In the aforementioned studies, pregnancy was evaluated as a single event, when, in reality, it has three distinct immunological phases that are characterized by distinct biological processes and can be symbolized by how the pregnant woman feels [29,38].

Implantation, placentation, and the first and early second trimester of pregnancy resemble “an open wound” that requires a strong inflammatory response. During this first stage, the blastocyst has to break through the epithelial lining of the uterus in order to implant; damage the endometrial tissue to invade; followed by the trophoblast replacement of the endothelium and vascular smooth muscle of the maternal blood vessels in order to secure an adequate placental-fetal blood supply [39]. All these activities create a veritable “battleground” of invading cells, dying cells, and repairing cells. An inflammatory environment is required in order to secure the adequate repair of the uterine epithelium and the removal of cellular debris [10,40]. Meanwhile, the mother’s well-being is clinically affected: she feels sick because her whole body is struggling to adapt to the presence of the fetus (in addition to hormone changes and other factors, this inflammatory response is responsible for “morning sickness”). Thus, the first trimester of pregnancy is a proinflammatory phase [29,41].

The second immunological phase of pregnancy is, in many ways, the optimal time for the mother. This is a period of rapid fetal growth and development. The mother, placenta, and fetus are symbiotic, and the predominant immunological feature is induction of an anti-inflammatory state. The woman no longer suffers from nausea and fever as she did in the first stage, in part, because the immune response is no longer the predominant endocrine feature.

Finally, during the last immunological phase of pregnancy, the fetus has completed its development; all the organs are functional and ready to deal with the external world. Now the mother needs to deliver the baby, and this can only be achieved through renewed inflammation. Parturition is characterized by an influx of immune cells into the myometrium in order to promote recrudescence of an inflammatory process [42,43]. This

proinflammatory environment promotes the contraction of the uterus, expulsion of the baby and rejection of the placenta. In conclusion, pregnancy is a proinflammatory and anti-inflammatory condition, depending upon the stage of gestation [44]–[45].

Inflammation and implantation

Embryo implantation, which is an absolute requirement for reproduction, starts with blastocyst apposition to the uterine endometrium, followed by its attachment to the endometrial surface epithelium. Implantation can only take place in a receptive uterus. In humans, the uterus becomes receptive during the midsecretory phase (days 19–23) of the menstrual cycle, commonly known as the window of implantation (WOI). Rodents exhibit a relatively short (4-day) estrous cycle and develop a receptive uterus on day 4 after mating [46].

The uterine endometrium consists of two distinct cellular components, the stromal cells and the cells of the epithelium. The cellular changes during the WOI include the transformation of the fibroblast-like endometrial stromal cells into larger and rounded decidual cells (decidualization) [47], as well as the growth and development of secretory glandules and the emergence of large apical protrusions (pinopodes) and microvilli on the luminal epithelium [48]. In parallel, modulations in the expression of different cytokines, chemokines, growth factors, and adhesion molecules take place [47,48]. These changes are subjected to regulation by the ovarian steroid hormones, 17β-estradiol and progesterone [49] [50].

The modulated expression of the above-mentioned molecules at the WOI provides circumstantial evidence for their role in this process. However, the association of some of these specific endometrial genes with impaired fertility in humans has not been consistent [50,51]. Moreover, global microarray analysis employed in search of implantation markers revealed a large number of genes expressed differentially in human endometrium during the WOI [52–55], providing correlative evidence for their possible involvement in implantation. Interestingly, many of those genes are of immunologic origin and have been called blastocyst implantation essential factors (BIEFs) [56]. However, their specific function has yet to be determined.

Tissue repair and implantation

Clinical studies have demonstrated that endometrial biopsies taken during the spontaneous cycle that preceded the in vitro fertilization (IVF) and embryo transfer (ET) treatment more than doubled the rates of implantation, clinical pregnancies and live births [57][58]. A more recent study further reported that local injury of the endometrium performed in IVF/ET patients during their cycle of treatment, before ovum retrieval, also resulted in increased success of implantation and pregnancy [59]. Mechanical manipulation, which is associated with decidual formation is not a new phenomenon. In 1907, Leo Loeb [60], first reported that scratching the guinea-pig uterus during the progestational phase of the estrous cycle provoked a rapid growth of decidual cells. Later experiments showed that decidua formation in pseudopregnant rodents could be induced by other forms of local injury, such as suturing the uterine horn [61] and intrauterine injection of oil [62]. These early observations in rodents, combined with recent findings in human patients, suggest that local injury of the endometrium facilitates successful implantation. Additionally, albeit indirect, evidence to support the beneficial effect of endometrial injury on successful implantation comes from the observation that scar tissue from previous endometrial surgery (or Cesarean section) becomes an attractive site of implantation [63]. Taken together, these reports suggest that it is possible that the success of implantation is secondary to the *development of an injury-like inflammatory reaction*.

Inflammation and immune cells during implantation

As discussed above, a high level of the proinflammatory T helper (Th)-1 and cytokines (IL-6, IL-8, TNFα) characterizes early implantation [38,64–67]. These cytokines can be secreted by the endometrial cells as well as by cells of the immune system that are recruited to the site of implantation. 65–70% are uterine-specific natural killer (NK) cells[68], and 10–20% are macrophages (Mos) and 2–4 % are dendritic cells (DCs) [10,11,68–72]. NK cells in human decidua have a role in regulating trophoblast invasion by the production of IL-8 and interferon-inducible protein-10 chemokines. Furthermore, decidual NK cells are potent secretors of an array of angiogenic factors that induce vascular growth that is essential for the establishment of an adequate decidua [45,73]. DCs are a heterogenous population of cells that initiate and coordinate the innate adaptive immune response. These cells accumulate in the pregnant uterus prior to implantation and stay in the decidua throughout pregnancy [74–76]. Several lines of evidence point to a pivotal role of macrophages and DCs in shaping the cytokine profile at the maternal–fetal interface [45,67,74]. Furthermore, in recent studies we showed that depletion of uterine DCs (uDCs) cells resulted in a severe impairment of implantation and led to embryo resorption [77]. However, the effect observed in our study was *not related to tolerance but rather to successful decidualization*. In agreement with these findings, another study showed that therapy with DCs significantly decreased the spontaneous resorption rate in a mouse model [74]. These studies, both suggest that, in addition to their involvement in the immune response, uDCs also play some trophic role in regulating the process of implantation.

The immune infiltrate, that plays a central role in the process of tissue renewal and differentiation, may also participate in the development of a receptive endometrium in the biopsy-treated patients [39]. In addition to their immediate influence, recruitment of cells of the immune system to the site of injury may create some “tissue memory” facilitating implantation in the following cycle of treatment. In fact, monocyte precursors of macrophages and DCs are known to be recruited to injured sites and provide essential beneficial effects during wound healing. These cells are long lived, and reside in some tissues for months, during which time they can differentiate into tissue-resident macrophages or DCs [78].

The trophoblast-lumen epithelium synapse

As the blastocyst travels from the fallopian tube to the uterine cavity, the surface epithelium of the uterus functions as the first contact responsible for adequate attachment of the trophectoderm to the epithelium and the subsequent trophoblast invasion and placentation. When a mammalian blastocyst enters the uterine cavity, the surface epithelium of the uterus is covered by molecules, such as Mucin 1 (MUC1) carbohydrates that prevent the attachment of the highly adhesive blastocyst to an improper site. Indeed, in the human endometrium MUC1 is upregulated during the implantation period [79,80]. This suggests that the human endometrial surface epithelium prevents blastocyst adhesion except for the precise spot were the embryo attaches. We hypothesize that cytokines/chemokines produced by DCs/Mo in the uterine stroma induce local degradation of MUC1 that enable the blastocyst to attach to a specific area of the uterus [39]. There are four ways by which blastocysts binding to the epithelium may be enhanced: i) stored adhesion molecules are rapidly moved to the cell surface; ii) inflammation-induced expression of new adhesion molecules; iii) increased affinity of specific molecules following initial cell contact; and iv) reorganization of adhesion molecules on the surface epithelium. Either of these possibilities or their combination can represent the response of the endometrial epithelium to DCs recruited to the site of implantation.

Conclusion

We propose a new paradigm in terms of the fetal-maternal immune interaction as well as the immunological response of the mother to micro-organism. In other words, the immunology of pregnancy is the result of the combination of signals and responses originating from the maternal immune system and the fetal-placental immune system. The signals originated in the placenta will modulate the way the maternal immune system will behave in the presence of potential dangerous signals [17]. Our challenge is to better understand this interaction in order to deliver the appropriate treatment to patients with pregnancy complications as well as to determine public policies for the protection of pregnant women during pandemics.

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References

1. Aluvihare VR, Kallikourdis M, Betz AG. Regulatory T cells mediate maternal tolerance to the fetus. Nat Immunol. 2004; 5:266–271. [PubMed: 14758358]
2. Bulmer JN, Pace D, Ritson A. Immunoregulatory cells in human decidua: morphology, immunohistochemistry and function. Reprod Nutr Dev. 1988; 28:1599–1613. [PubMed: 3073448]
3. Zenclussen AC. CD4(+)CD25+ T regulatory cells in murine pregnancy. J Reprod Immunol. 2005; 65:101–110. [PubMed: 15811515]
4. King A, Loke YW, Chaouat G. NK cells and reproduction. Immunol Today. 1997; 18:64–66. [PubMed: 9057355]
5. Mor G, Straszewski-Chavez SL, Abrahams VM. Macrophage-trophoblast interactions. Methods Mol Med. 2006; 122:149–163. [PubMed: 16511980]
6. Wicherek L, et al. The characterization of the subpopulation of suppressive B7H4(+) macrophages and the subpopulation of CD25(+) CD4(+) and FOXP3(+) regulatory T-cells in decidua during the secretory cycle phase, Arias Stella reaction, and spontaneous abortion - a preliminary report. Am J Reprod Immunol. 2009; 61:303–312. [PubMed: 19260861]
7. Shimada S, et al. Natural killer, natural killer T, helper and cytotoxic T cells in the decidua from sporadic miscarriage. Am J Reprod Immunol. 2006; 56:193–200. [PubMed: 16911715]
8. Ashkar AA, Di Santo JP, Croy BA. Interferon gamma contributes to initiation of uterine vascular modification, decidual integrity, and uterine natural killer cell maturation during normal murine pregnancy. J Exp Med. 2000; 192:259–270. [PubMed: 10899912]
9. Greenwood JD, et al. Ultrastructural studies of implantation sites from mice deficient in uterine natural killer cells. Placenta. 2000; 21:693–702. [PubMed: 10985973]
10. Abrahams VM, et al. Macrophages and apoptotic cell clearance during pregnancy. Am J Reprod Immunol. 2004; 51:275–282. [PubMed: 15212680]
11. Le Bouteiller P, Piccinni MP. Human NK cells in pregnant uterus: why there? Am J Reprod Immunol. 2008; 59:401–406. [PubMed: 18405310]
12. Hanna J, et al. Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. Nat Med. 2006; 12:1065–1074. [PubMed: 16892062]
13. Manaseki S, Searle RF. Natural killer (NK) cell activity of first trimester human decidua. Cell Immunol. 1989; 121:166–173. [PubMed: 2785865]
14. Blois SM, et al. A pivotal role for galectin-1 in fetomaternal tolerance. Nat Med. 2007; 13:1450–1457. [PubMed: 18026113]
15. Birnberg T, et al. Dendritic cells are crucial for decidual development during embryo implantation. Am J Reprod Immunol. 2007; 57:342.
16. Collins MK, Tay CS, Erlebacher A. Dendritic cell entrapment within the pregnant uterus inhibits immune surveillance of the maternal/fetal interface in mice. J Clin Invest. 2009; 119:2062–2073. [PubMed: 19546507]

17. Mor G, Cardenas I. The Immune System in Pregnancy: A Unique Complexity. Am J Reprod Immunol. 2010; 63:425–433. [PubMed: 20367629]
18. Szekeres-Bartho J, Polgar B. PIBF: the double edged sword. Pregnancy and tumor. Am J Reprod Immunol. 2010; 64:77–86. [PubMed: 20367622]
19. Cardenas I, et al. Viral infection of the placenta leads to fetal inflammation and sensitization to bacterial products predisposing to preterm labor. J Immunol. 2010; 185:1248–1257. [PubMed: 20554966]
20. Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. American Journal of Reproductive Immunology. 2010; 63:425–433. [PubMed: 20367629]
21. Medawar PB. Immunity to homologous grafted skin. III. The fate of skin homografts transplanted to the brain, to subcutaneous tissue, and to the anterior chamber of the eye. British Journal of Experimental Pathology. 1948; 29:58–69. [PubMed: 18865105]
22. Medawar P. Some immunological and endocrinological problems raised by the evolution of viviparity in vertebrates. Symp Soc Exp Biol. 1952; 7:320–338.
23. Saito, S.; Miyazaki, S.; Sasaki, Y. Th1/Th2 balance of the implantation site in humans. Landes Bioscience/Springer Science; Georgetown, Texas: 2006.
24. Loke YW, King A. Immunology of implantation. Baillieres Best Pract Res Clin Obstet Gynaecol. 2000; 14:827–837. [PubMed: 11023803]
25. Leber A, Teles A, Zenclussen AC. Regulatory T cells and their role in pregnancy. Am J Reprod Immunol. 2010; 63:445–459. [PubMed: 20331584]
26. Petroff MG, Perchellet A. B7 family molecules as regulators of the maternal immune system in pregnancy. Am J Reprod Immunol. 2010; 63:506–519. [PubMed: 20384620]
27. Mincheva-Nilsson L, Baranov V. The role of placental exosomes in reproduction. Am J Reprod Immunol. 2010; 63:520–533. [PubMed: 20331583]
28. Mor G, et al. Is the trophoblast an immune regulator? The role of Toll-like receptors during pregnancy. Crit Rev Immunol. 2005; 25:375–388. [PubMed: 16167887]
29. Mor G. Pregnancy Reconceived. Natural History. 2007; 116:36–41.
30. Mor G, et al. Is the trophoblast an immune regulator?: the role of toll-like receptors during pregnancy. Crit Rev Immunol. 2005; 25:375–388. [PubMed: 16167887]
31. Fest S, et al. Trophoblast-macrophage interactions: a regulatory network for the protection of pregnancy. Am J Reprod Immunol. 2007; 57:55–66. [PubMed: 17156192]
32. Abrahams VM, et al. A role for TLRs in the regulation of immune cell migration by first trimester trophoblast cells. J Immunol. 2005; 175:8096–8104. [PubMed: 16339547]
33. Aldo PB, et al. A novel three-dimensional in vitro system to study trophoblast-endothelium cell interactions. Am J Reprod Immunol. 2007; 58:98–110. [PubMed: 17631003]
34. Wegmann T. Fetal protection against abortion: Is it immunosupression or immunostimulation? Ann Immunol. 1984; 135D:309–312.
35. Szekeres-Bartho J, Wegmann TG. A progesterone-dependent immunomodulatory protein alters the Th1/Th2 balance. J Reprod Immunol. 1996; 31:81–95. [PubMed: 8887124]
36. Wegmann TG, et al. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon? Immunol Today. 1993; 14:353–356. [PubMed: 8363725]
37. Saito S, et al. Th1/Th2/Th17 and regulatory T-cell paradigm in pregnancy. Am J Reprod Immunol. 2010; 63:601–610. [PubMed: 20455873]
38. Mor G, Koga K. Macrophages and pregnancy. Reprod Sci. 2008; 15:435–436. [PubMed: 18579852]
39. Dekel N, et al. Inflammation and implantation. Am J Reprod Immunol. 2010; 63:17–21. [PubMed: 20059465]
40. Koga K, Mor G. Toll-like receptors at the maternal-fetal interface in normal pregnancy and pregnancy disorders. Am J Reprod Immunol. 2010; 63:587–600. [PubMed: 20367625]
41. Mor, G.; Abrahams, V. Immunology of Implantation. In: Arici, A., editor. Immunology and Allergy Clinics. Vol. 22. W.B. Saunders Company; Philadelphia: 2002. p. 545-565.

42. Romero R, et al. The preterm parturition syndrome. BJOG. 2006; 113(Suppl 3):17–42. [PubMed: 17206962]
43. Romero R, et al. Inflammation in preterm and term labour and delivery. Semin Fetal Neonatal Med. 2006; 11:317–326. [PubMed: 16839830]
44. Romero R. Novel aspects of neutrophil biology in human pregnancy. Am J Reprod Immunol. 2005; 53:275.
45. Mor G. Inflammation and pregnancy: the role of toll-like receptors in trophoblast-immune interaction. Ann N Y Acad Sci. 2008; 1127:121–128. [PubMed: 18443339]
46. Wang H, Dey SK. Roadmap to embryo implantation: clues from mouse models. Nat Rev Genet. 2006; 7:185–199. [PubMed: 16485018]
47. Dunn CL, Kelly RW, Critchley HO. Decidualization of the human endometrial stromal cell: an enigmatic transformation. Reprod Biomed Online. 2003; 7:151–161. [PubMed: 14567882]
48. Paria BC, RJ, Das SK, Dey SK. Deciphering the cross-talk of implantation: advances and challenges. Science. 2002; 296:2185–2188. [PubMed: 12077405]
49. Dunn CL, KR, Critchley HO. Decidualization of the human endometrial stromal cell: an enigmatic transformation. Reprod Biomed. 2003; 7:151–161.
50. Akbas GE, TH. HOXC and HOXD gene expression in human endometrium: lack of redundancy with HOXA paralogs. Biol Reprod. 2004; 70:39–45. [PubMed: 12954737]
51. Kao LC, TS, Lobo S, Imani B, Yang JP, Germeyer A, Osteen K, Taylor RN, Lessey BA, Giudice LC. Global gene profiling in human endometrium during the window of implantation. Endocrinology. 2002; 143:2119–2138. [PubMed: 12021176]
52. Popovici RM, KL, Giudice LC. Discovery of new inducible genes in in vitro decidualized human endometrial stromal cells using microarray technology. Endocrinology. 2000; 141:3510–3513. [PubMed: 10965925]
53. Carson DD, LE, Thathiah A, Al-Shami R, Farach-Carson MC, Vernon M, Yuan L, Fritz MA, Lessey B. Changes in gene expression during the early to mid-luteal (receptive phase) transition in human endometrium detected by high-density microarray screening. Mol Hum Reprod. 2002; 8:871–879. [PubMed: 12200466]
54. Dominguez F, RJ, Pellocer A, Simon C. Human endometrial receptivity: a genomic approach. Reprod Biomed Online. 2003; 6:332–338. [PubMed: 12735869]
55. Giudice L. Microarray expression profiling reveals candidate genes for human uterine receptivity. Am J Pharmacogenomics. 2004; 4:299–312. [PubMed: 15462608]
56. Yoshinaga K. Research on Blastocyst Implantation Essential Factors (BIEFs). Am J Reprod Immunol. 2010; 63:413–424. [PubMed: 20455874]
57. Barash A, DN, Fieldust S, Segal I, Schechtman E, Granot I. Local injury of the endometriumdoubles the incidence of successful pregnancies in patients undergoing in-vitro fertilization. Fertil Steril. 2003; 79:1317–1322. [PubMed: 12798877]
58. Raziel A, SM, Strassburger D, Berno O, Ron-El R, Friedler S. Favorable influence of local injury to the endometrium in intracytoplasmic sperm injection patients with high-order implantation failure. Fertil Steril. 2007; 87:198–201. [PubMed: 17197286]
59. Zhou L, LR, Wang R, Huang HX, Zhong K. Local injury to the endometrium in controlled ovarian hyperstimulation cycles improves implantation rates. Fertil Steril. 2008; 89:1166–1176. [PubMed: 17681303]
60. Loeb L. Ueber die experimentelle Erzeugung von Knoten von Deciduagewebe in dem Uterus des Meerschweinchens nach stattgefundener. Copulation Zentralbl AIIg Pathol Pathol Anat. 1907; 18:563–565.
61. Turner, CD.; BJ. Biological effects of the ovarian hormones. In: WB, S., editor. General endocrinology. Philadelphia: Pennsylvania; 1976. p. 466-476.
62. Saito, S.; MS; Sasaki, Y. Th1/Th2 balance at implantation stage. In: GM, editor. Immunology of pregnancy. New York, New York: 2006. p. 37-48.
63. Dominguez F, et al. Embryonic implantation and leukocyte transendothelial migration: different processes with similar players? Faseb J. 2005; 19:1056–1060. [PubMed: 15985528]

64. Koga K, Mor G. Expression and function of toll-like receptors at the maternal-fetal interface. Reprod Sci. 2008; 15:231–242. [PubMed: 18421019]

65. Yoshinaga K. Review of factors essential for blastocyst implantation for their modulating effects on the maternal immune system. Semin Cell Dev Biol. 2008; 19:161–169. [PubMed: 18054836]

66. Thaxton JE, Sharma S. Interleukin-10: a multi-faceted agent of pregnancy. Am J Reprod Immunol. 2010; 63:482–491. [PubMed: 20163400]

67. Jasper MJ, et al. Macrophage-Derived LIF and IL1B Regulate alpha(1,2)Fucosyltransferase 2 (Fut2) Expression in Mouse Uterine Epithelial Cells During Early Pregnancy. Biol Reprod. 2010

68. Manaster I, Mandelboim O. The unique properties of uterine NK cells. Am J Reprod Immunol. 2010; 63:434–444. [PubMed: 20055791]

69. Hanna J, G-WD, Hamani Y, Avraham I, Greenfield C, Natanson-Yaron S, Prus D, Cohen-Daniel L, Arnon TI, Manaster I, Gazit R, Yutkin V, Benharroch D, Porgador A, Keshet E, Yagel S, Mandelboim O. Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. Nat Med. 2006; 12:1065–1074. [PubMed: 16892062]

70. Kammerer, U., et al. Characterization of human dendritic cells at the materno-fetal interface. Landes Bioscience/Springer Science; Georgetown, Texas: 2006.

71. Roussev RG, et al. Duration of intralipid's suppressive effect on NK cell's functional activity. Am J Reprod Immunol. 2008; 60:258–263. [PubMed: 18782287]

72. Nagamatsu T, Schust DJ. The contribution of macrophages to normal and pathological pregnancies. Am J Reprod Immunol. 2010; 63:460–471. [PubMed: 20163399]

73. Burke SD, et al. Uterine NK cells, spiral artery modification and the regulation of blood pressure during mouse pregnancy. Am J Reprod Immunol. 2010; 63:472–481. [PubMed: 20175772]

74. Laskarin G, KU, Rukavina D, Thomson AW, Fernandez N, Blois SM. Antigen-presenting cells and materno-fetal tolerance: an emerging role for dendritic cells. Am J Reprod Immunol. 2007; 58:255–267. [PubMed: 17681042]

75. Kämmerer U. Antigen-presenting cells in the decidua. Chem Immunol Allergy. 2005; 89:96–104. [PubMed: 16129956]

76. Scholz C, et al. Glycodelin A induces a tolerogenic phenotype in monocyte-derived dendritic cells in vitro. Am J Reprod Immunol. 2008; 60:501–512. [PubMed: 19032611]

77. Plaks V, et al. Uterine DCs are crucial for decidua formation during embryo implantation in mice. J Clin Invest. 2008; 118:3954–3965. [PubMed: 19033665]

78. Luster AD, AR, von Andrian UH. Immune cell migration in inflammation: present and future therapeutic targets. Nat Immunol. 2005; 6:1182–1190. [PubMed: 16369557]

79. Meseguer M, et al. Human endometrial mucin MUC1 is up-regulated by progesterone and down-regulated in vitro by the human blastocyst. Biol Reprod. 2001; 64:590–601. [PubMed: 11159362]

80. Simon C, et al. Embryonic regulation of endometrial molecules in human implantation. J Reprod Fertil Suppl. 2000; 55:43–53. [PubMed: 10889833]

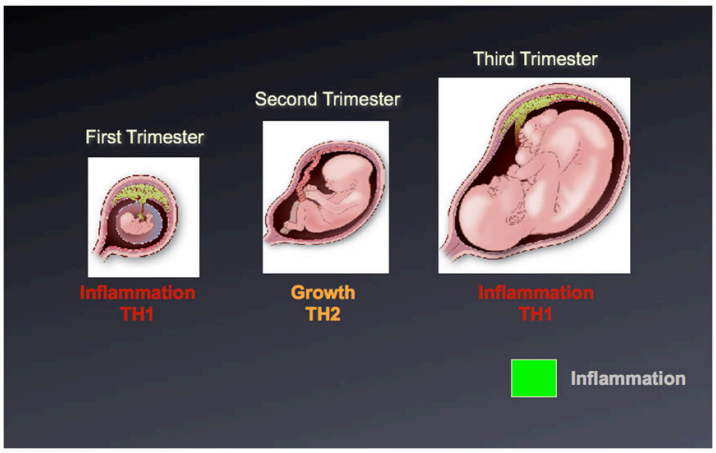

Figure 1. Trophoblast immune interactions

Three stages of interaction. Recruitment :1) Trophoblast sends signals to recruit immune cells towards the implantation site. 2) Education: trophoblast influence the differentiation of immune cells. 3) Response: factors produced by trophoblast-educated immune cells support placental formation and function.

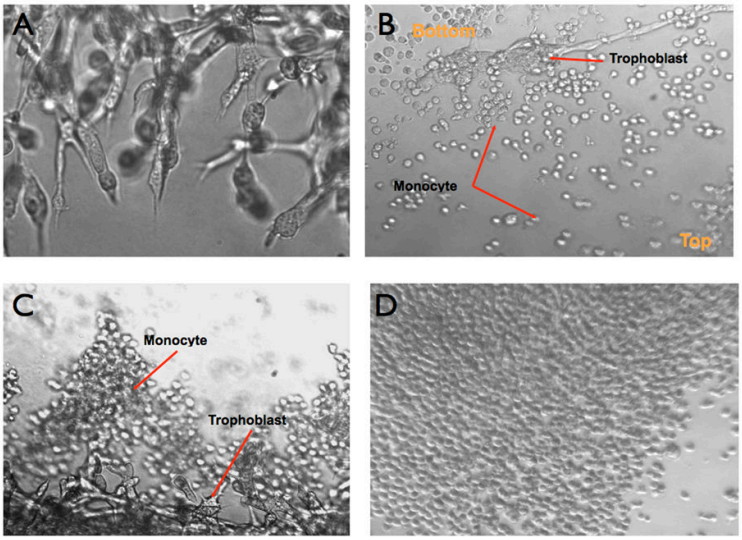

Figure 2. Recruitment of monocytes towards trophoblast cells

In vitro model for the study of trophoblast-immune interactions [33]. **A.** trophoblast cells form villi-like structures in Matrigel as previously described [33]. **B.** Monocytes are plated in the top of Matrigel and their movement monitored by in vivo imaging. Note monocyte/macrophage migration from the top of the gel towards trophoblast cells (Bottom). **C.** Monocyte/macrophage distribution is observed around trophoblast villi-like structures. **D.** In the absence of trophoblast cells, monocytes/macrophage accumulates in the top of the gel.

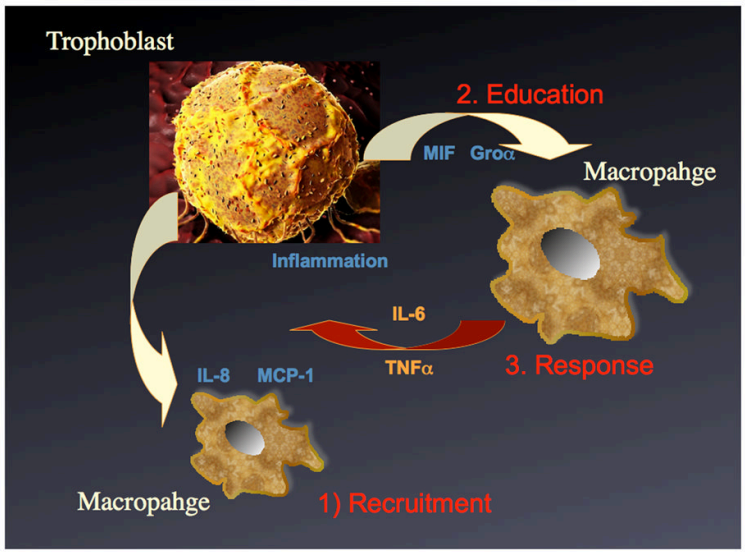

Figure 3. Immunologic phases of pregnancy

Each stage of pregnancy is characterized by a unique inflammatory environment. The first and third trimesters are proinflammatory (TH1), whereas the second trimester represents an anti-inflammatory phase also knowns and TH2 environment.