

The immunology of unexplained recurrent spontaneous abortion: cytokines as key mediators

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Spontaneous abortion is one of the most common complications of pregnancy. Recurrent spontaneous abortion (RSA), defined as the occurrence of three consecutive abortions, occurs due to several identifiable causes such as anatomic, genetic, endocrinologic and infectious etiologies, but a substantial proportion of RSA, up to 50-60%, are due to unexplained or unknown etiologies. Of the various humoral immune etiologies that have been investigated, only anti-phospholipid antibodies have been confirmed as being etiologic factors, but that too, in a small proportion of the cases of RSA. Cellular immune effectors and cytokines have been the focus of intense investigation recently, and it appears that certain cytokines may be beneficial to pregnancy, while some are actually antagonistic to pregnancy. This article reviews recent observations on the association between cytokines and unexplained recurrent spontaneous abortion.

Evidence from studies on murine and human pregnancy points to a strong association between maternal Th2-type immunity and successful pregnancy on the one hand and between Th1-type immune reactivity and pregnancy loss on the other. While there is a paucity of data from human pregnancy indicating that Th1-type immune effectors actually lead to pregnancy, it is difficult to ignore the compelling evidence linking inappropriate Th1-type immunity to pregnancy loss. Th2-type immunity may play protective roles during pregnancy, hence the nexus between a Th2 shift and successful pregnancy. This article examines these associations and discusses possible mechanisms underlying immunologically-mediated pregnancy failure.

Key words: Recurrent spontaneous abortion, cytokines, pregnancy loss

Bull Kuwait Inst Med Spec 2003;2:32-38

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Introduction

Pregnancy is not nearly as successful as one might think; fetal viability is not achieved in approximately 70% of human conceptions and an estimated 50% are lost prior to the first missed menses.¹ In fact, the actual rate of early pregnancy loss after implantation may

exceed the number of recognized pregnancies, and may be as high as 31%. Spontaneous abortion, defined as a clinically detectable pregnancy loss prior to 20 weeks of gestation, occurs at a frequency of 15% to 25%. Spontaneous abortion is one of the most common complications of pregnancy, with approximately one in every four pregnant women undergoing one or more pregnancy losses.² For most women, spontaneous abortion is a random event, but some women have three or more consecutive abortions, and these women are recognized as having *recurrent spontaneous abortion* (RSA), defined as the occurrence of 3 or more clinically detectable pregnancy losses before the 20th week of gestation. Causation is usually sought after two consecutive pregnancy losses, especially for couples without a successful pregnancy where fetal heart activity has been identified, in couples where the woman is older than 35 years of age, and in couples having difficulty conceiving.

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Etiologies of Recurrent Spontaneous Abortion

The search for etiologies of RSA have led to the current estimates (Table 1) of the proportion of RSA caused by chromosomal anomalies,³ endocrinologic abnormalities,⁴ infectious⁵ and anatomic⁶ problems, and by humoral anti-phospholipid antibodies.⁷

Table 1. Etiology of Recurrent Spontaneous Abortion

Factor	Incidence (%)
Endocrine	17
Anatomic	10
Genetic	5
Infectious	5
Anti-phospholipid antibodies	3
Unknown etiology	60

As can be seen in Table 1, the currently well-established mechanisms together account for only about 40% of the cases of RSA, with a substantial proportion of cases classified as "unknown" or "unexplained".⁸ The existence of such a large proportion of cases with unidentified etiologies has in part fuelled great interest in the investigation of possible immunologic etiologies of pregnancy failure.

At least three lines of evidence suggest that immunologic causes may account for a proportion of the previously unexplained pregnancy losses. One is the impressive capacity of the immune system to effect various deleterious reactions such as allograft rejection, hypersensitivity and autoimmune tissue damage. Secondly, female reproductive tissues are immunologically dynamic; just as the immune system interacts dynamically with other systems in the body, bi-directional 'cross-talk' occurs between the immune system and the reproductive system during pregnancy. In fact, there is evidence to suggest that not only is the maternal immune system not oblivious to the fetus, it promotes placental growth and function, thereby enhancing fetal survival and development. Therefore, thirdly, as a corollary to the conducive effects of maternal immunity, other cell-mediated reactions involving maternal T cells, macrophages, natural killer cells, and cytokines, may actually culminate in pregnancy failure.

Several humoral immune effectors of RSA have been proposed over the years (Table 2).

Table 2. Proposed humoral immune factors in RSA

Anti-phospholipid antibodies
Anti-sperm antibodies
Anti-trophoblast antibodies
Deficiency of blocking antibodies

Of these, only anti-phospholipid antibodies have been well substantiated as etiologic agents. Anti-phospholipid antibody syndrome is defined as the production of autoantibodies against negatively charged phospholipids, clinically associated with thrombocytopenia, thrombosis, pregnancy loss or a combination of these events.⁹ Patients with this syndrome have a pregnancy loss rate of about 50%, with some studies indicating a rate as high as 80-90%. The predominant hypothesis for the role of these antibodies in causing placental damage is decidual-placental thrombosis commonly observed in this syndrome. Thrombosis is not seen in all patients, and it is proposed that anti-phospholipid antibodies bind to externalized phospholipid antigens on the trophoblast and cause incomplete differentiation of the trophoblast and/or direct damage to the trophoblast.¹⁰ However, even antiphospholipid antibodies are estimated to be responsible for RSA in only about 3% of the cases of RSA.⁷ Thus anti-phospholipid antibodies do not appear to be major etiologic factors in recurrent abortion.

Cell-mediated Immunity and RSA

Interestingly, the conceptus appears to be fairly impervious to attack by humoral immunity except for anti-phospholipid antibodies. This then raises the possibility of cell-mediated immune effectors, including cells and cytokines, as possible etiologic agents in RSA. Cellular immunity have been shown to be linked to deleterious effects on the conceptus (Table 3).

Table 3. Cell-mediated immune effectors and pregnancy failure

Fetal resorption sites in murine models of immunologically-mediated pregnancy failure are infiltrated by natural killer (NK) cells.
Immunologically-mediated pregnancy loss in mice can be prevented by antibodies to NK cells.
Fetal resorption sites in mice are infiltrated by activated macrophages; embryo loss is associated with local production of nitric oxide by macrophages.
Placental trophoblast cells are sensitive to lysis by lymphokine-activated killer cells and activated NK cells.

Cytokines and RSA

It has been proposed that effector cells may actually exert their deleterious effects on the conceptus via the secretion of cytokines; what are cytokines? The broadest definition of cytokines is that they are soluble proteins that affect the behavior of other cells, or soluble proteins which mediate interactions between cells. More specifically, *cytokines are numerous secreted proteins that regulate the intensity and duration of immune responses by exerting a variety of effects on lymphocytes and other cells.* These intercellular messenger molecules mediate a whole range of cellular functions such as the induction of humoral and cellular immunity, inflammation, cellular proliferation and differentiation, inhibition of growth, apoptosis, wound healing and perhaps many, many more activities.

That several cytokines can be detrimental to pregnancy has been established beyond reasonable doubt, as depicted by the lines of evidence presented in Table 4.

Table 4. Cytokines deleterious to the conceptus

The administration of tumor necrosis factor- α (TNF α), interferon γ (IFN γ) and interleukin (IL)-2 into pregnant mice causes abortions. ¹¹
Low doses of anti-TNF α antibodies reduce resorption rates in a murine abortion model. ¹¹
A strong murine anti-parasite response which includes high placental levels of IFN γ and TNF α is accompanied by fetal resorption. ¹²
TNF α and IFN γ inhibit outgrowth of human trophoblast cells <i>in vitro</i> . ¹³
TNF α and IFN γ stimulate the programmed death of human primary villous trophoblast cells. ¹⁴

It is interesting that the cytokines that appear to be most harmful to the conceptus, i.e. IFN γ , IL-2 and TNF α , together fit the profile of T helper (Th) 1 cells. What are Th1 cells?

Th1/Th2 Cytokines and RSA

One of the most significant recent advances in our understanding of immune responses has been the delineation of the T helper 1/T helper 2 paradigm which provides a framework for understanding how the immune system directs responses to different types of pathogens. The two major subsets of CD4⁺ T helper cells, Th1 and Th2, have different patterns of cytokine production and different roles in immune responses. Each subset induces functions that are effective at handling certain types of pathogens, but can be ineffective, or even pathological if made in response

to other types of pathogens.^{16,17} Th1 cells secrete the cytokines IL-2, IFN γ , TNF β and TNF α . Th1-type cytokines activate macrophages and cell-mediated reactions important in resistance to infection with intracellular pathogens, and in cytotoxic and delayed-type hypersensitivity (DTH) reactions. Th2 cells secrete the cytokines IL-4, IL-5, IL-6, IL-10 and IL-13 which encourage vigorous antibody production, and are therefore commonly associated with strong antibody responses that are important in combating infections with extracellular organisms. Th1 and Th2 cells are mutually inhibitory to each other; when Th1 reactivity is high, Th2 reactivity is usually low and vice versa.

Since several cell types besides T helper cells contribute to an overall Th1 or Th2 cytokine pattern, it has been suggested that these responses should instead be described as type 1 or type 2. Which type of reactivity, type 1 or type 2, is activated first may influence the subsequent outcome; if a particular T cell subset is activated first or preferentially in a response, it can suppress the development of the other subset. The overall effect is that immune responses are often dominated by either humoral (type 2) or cell-mediated (type 1) immunity.

The data presented in Tables 3 and 4 correlate well with the contention that a strong, maternal Th1-type or type 1 reactivity is deleterious to the conceptus.^{13,14,17,18} If Th1-type cytokines are indeed deleterious to pregnancy, the corollary is that Th2-type cytokines may be favourable to pregnancy, and thus Th2-type or type 2 immunity has been proposed to be the profile of normal, successful pregnancy.¹⁹ Another line of evidence that supports the Th1-Th2 paradigm in pregnancy is the observation that the predominant maternal immune response during pregnancy is humoral, and not cell-mediated,²⁰ unlike the conventional host anti-graft response which is primarily a strong cell-mediated rejection reaction. Pregnancy appears to confer some resistance to the induction of cellular responses such as the induction of DTH and NK activity. Interestingly, intracellular infections such as leprosy, tuberculosis, toxoplasmosis and malaria are often exacerbated during gestation (reviewed in 19). Furthermore, cell-mediated autoimmune diseases such as rheumatoid arthritis tend to improve during hu-

man pregnancy, while the antibody-mediated disease systemic lupus erythematosus tends to be aggravated, indicating a weakening of cell-mediated immunity and an enhancement of antibody responses during pregnancy; this correlates with a down-regulation of Th1-type activity and an enhancement of Th2-type reactivity.

Recent studies on RSA support the concept that successful pregnancy occurs in a Th2-biased situation, while Th1-type immunity may lead to pregnancy failure. Studies in Hill's laboratory at the Harvard Medical School have shown that peripheral blood mononuclear cells (PBMC) of women with a history of RSA when stimulated with a trophoblast antigen extract produce higher levels of the type 1 cytokines and embryotoxic activity as compared to normal pregnancy.²¹ Embryotoxic activity was detected in 66% of patients with unexplained RSA and in none of the controls, and IFN γ production correlated well with embryotoxic activity. In addition, a majority of the RSA samples tested positive for the Th1 cytokines TNF β and TNF α , and the majority negative for the Th2 cytokines IL-4 and IL-10. In contrast, PBMC supernatants from reproductively normal women were not embryotoxic nor did they contain type 1 cytokines, but they all contained IL-10. These authors conclude that type 1 immunity to trophoblast antigens is associated with unexplained recurrent abortion and may play a role in reproductive failure while type 2 immunity may be the natural maternal immune response to the trophoblast, thus contributing to successful pregnancy. That this is mirrored by the situation at the maternal-fetal interface was shown by Piccinni and colleagues at the University of Florence in Italy when they demonstrated significantly higher levels of IL-4 and IL-10-producing T cell clones from the decidua of women with normal pregnancy than those from recurrent aborters.²²

Work conducted by us at the Faculty of Medicine has taken these observations further; we first showed that women with a history of successful pregnancy have a bias towards Th2-type immunity, while women with RSA have a dominant Th1-type reactivity, as reflected by the cytokine secretion profiles of mitogen-stimulated peripheral lymphoid cells and the ratios of Th1 to Th2 cytokines. PBMC

obtained from normal pregnant women at the end of the first trimester and at delivery, and from recurrent aborters at the time of abortion, were stimulated with a mitogen and the supernatants tested for type 1 and type 2 cytokines. Levels of the Th2-type cytokines IL-4, IL-5, IL-6 and IL-10 were consistently higher at the end of the first trimester and at delivery in normal pregnancy than in RSA, while the levels of IL-2, IFN γ and TNF α were uniformly higher in RSA than in normal pregnancy.^{23,24} Since the absolute concentrations of secreted cytokines may not be indicative of a type 1- or type 2-bias *per se*, we analyzed the ratios of type 1 to type 2 cytokines in the various permutations. In every combination of type 1 to type 2 cytokines, the ratios were higher in the RSA group as compared to the normal pregnancy group, indicating a greater type 1-bias in RSA and a greater type 2-bias in normal pregnancy.

Besides demonstrating type 1-bias in mitogen-stimulated, 'non-specific' maternal reactivity, we also examined 'specific' responses of maternal lymphocytes to autologous placental cells and to trophoblast antigens. Specific maternal reactivity to placental antigens was assessed by co-culturing maternal PBMC with autologous placental cells in a mixed lymphocyte-placenta reaction technique. Stimulation of maternal cells by irradiated autologous placental cells was followed by the measurement of relevant type 1 and type 2 cytokines. PBMC from the RSA group secreted significantly higher levels of IFN γ and lower levels of IL-6 IL-10 as compared to women in the normal pregnancy group.²⁵

In human pregnancy loss, studies to date indicate a correlation between the type of maternal immune reactivity and the outcome of pregnancy, without a definitive cause-and-effect relationship, though studies on animals have shown that the injection of type 1 cytokines results in abortions.¹¹ One study that comes closer to a cause-and-effect relationship is the one in which cytokine production was tested 1-2 weeks before any upcoming pathology could be detected showing decreased production of IL-4 and IL-10 and increased production of IFN- γ and IL-2 by antigen-stimulated PBMC from women with RSA as opposed to those from normal pregnancy.

Effects of Cytokines on the Conceptus

How might type 1 or Th1 reactivity affect the conceptus? Increased blood and uterine NK activity has been linked to abortion and increased NK activity in the blood has been shown to be predictive of RSA.²⁷ While direct cell-mediated lysis is unlikely to cause trophoblast damage, as the trophoblast has been shown to be resistant to killing by cytotoxic T lymphocytes, conventional NK cells and conventional macrophages. It has been proposed that NK cells, like Th1 cells, could release cytokines deleterious to the trophoblast. Pro-inflammatory cytokines may convert NK cells into lymphokine-activated killer cells that have been shown to lyse trophoblast cells. Another cell type that may effect damage is the decidual macrophage; a correlation has been demonstrated between the triggering of cytotoxin production by primed decidual macrophages and early embryo loss.²⁸ For their part, activated macrophages may bring about damage to the conceptus not by direct lysis of trophoblast cells, but by the production of dangerous levels of nitric oxide and TNF α . The relevance of type 1 cytokines in this scenario would be to activate such cellular effectors and to also cause damage to the placenta, and the role of type 2 cytokines would be to suppress the Th1-NK-macrophage system. Direct effects of type 1 cytokines may include the apoptosis of trophoblast cells by TNF α and IFN γ ¹⁴, inhibition of secretion of the growth-stimulating cytokines from the uterine epithelium and cytokine-induced activation of coagulation mechanisms, which may then lead to vasculitis affecting maternal blood supply to the implanted embryo.

How is type 2-bias maintained in pregnancy? Cytokines, hormones and other molecules are likely to play critical roles in directing the immune reactivity towards a type 2 bias and then maintaining it in that fashion. IL-10 is probably one of the crucial cytokines responsible for maintaining a type 2 bias, once it is established; it interferes with antigen presentation, downregulates cytokine production by Th1 cells and inhibits NK responses.¹⁵ Interestingly enough, the cytotrophoblast and syncytiotrophoblast have been shown to preferentially produce IL-10 in a

gestational age-dependent manner, and it is possible that IL-10 produced in the placenta may play vital roles in counteracting deleterious inflammatory cytokines. Pregnancy-related hormones may also play decisive roles; progesterone has been shown to favour the development of human T cells producing type 2 cytokines, and Piccinni and colleagues²⁹ propose that progesterone may therefore be responsible at least in part for a type 1 \rightarrow type 2 switch at the maternal-fetal interface.

Immunomodulatory Therapy of RSA: Future Prospects

Recognition of the contrasts between Th1 and Th2 responses in disease states has suggested the therapeutic possibilities of manipulating Th1/Th2 balance in diseases with the objective of eliciting responses of the appropriate subset. In general, in addition to performing different tasks in immune defences when dysregulated, Th1 and Th2 responses may also lead to different types of immunopathologic conditions. Several laboratories are now engaged in pursuing novel opportunities for therapeutic intervention aimed at modulating or rectifying the Th1/Th2 balance. A wide range of approaches is being researched from this perspective, targeting cytokines, cytokine receptors, intracellular signalling pathways and transcription factors that control Th1 and Th2 differentiation. Efforts are also focused on the identification of selective markers for monitoring and altering Th1/Th2 cell distribution or function *in vivo*.

Thus, the exciting prospect of redirecting or modulating Th1 dominance offers hope for bringing about an immunological milieu that is more conducive to successful pregnancy.

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CME Questions

After you have completed reading the above article, take the test given below. Circle T (True) or F (False) in the answer sheet (page 50) to show the correct answer to each question. Questions 21 to 30 are related to the content in this article.

21. Th1 and Th2 cells can be distinguished on the basis of the cytokines produced by them.
22. The Th2 cytokines IL-4 and IL-10 appear to have anti-pregnancy effects.
23. Progesterone upregulates the production of the Th1 cytokines interferon- γ .
24. While Th1 and Th2 cytokines produce different cytokines, their functions are the same.
25. Th1 cells generally induce humoral immune responses, while Th2 cells promote cell-mediated immunity.
26. Anti-phospholipid antibodies account for most of the cases of recurrent spontaneous abortion.
27. Humoral antibody mechanisms are not the main factors underlying unexplained recurrent abortion.
28. Cytokines are cell-surface molecules that mediate adhesion between cells.
29. Cytokines are soluble factors that mediate a whole range of immunological processes.
30. Th1 reactivity is associated with unexplained RSA, while Th2 reactivity is associated with normal pregnancy.