Current Medicine Research and Practice 6 (2016) 233–239

Contents lists available at ScienceDirect

Current Medicine Research and Practice

journal homepage: www.elsevier.com/locate/cmrp

Review Article

Immunomodulation with progestogens as a therapeutic approach in pregnancy complications

Raj Raghupathy

Department of Microbiology, Faculty of Medicine, Kuwait University, PO Box 24923, Safat, Kuwait

ARTICLE INFO

Article history:
Received 23 September 2016
Accepted 25 October 2016
Available online 3 December 2016

Keywords:
Pregnancy
Recurrent spontaneous miscarriage
Progesterone
Dydrogesterone
Cytokines

ABSTRACT

Pregnancy is confronted with several challenges such as threatened abortion, spontaneous miscarriage, preeclampsia and preterm delivery. Immunologic effectors have been implicated as contributing to the etiopathogenesis of some of these pregnancy complications. Pro-inflammatory and anti-inflammatory cytokines have been investigated for their effects on the conceptus and pregnancy because of their wide-ranging and potent effects on cells and tissues. This review addresses the nexus between pro-inflammatory cytokines and recurrent miscarriage, which is an important complication of pregnancy. It summarizes the possible mechanisms of action of pro-inflammatory cytokines in pregnancy loss, and then proceeds to discuss immunomodulation of cytokine profiles to a state that is favourable to the success of pregnancy. Fascinating leads for possible redirection of cytokine profiles have come from observations on the immunomodulatory capabilities of progesterone. This review presents studies that show that progesterone and the orally-administered progestogen dydrogesterone inhibit pro-inflammatory cytokines and upregulate anti-inflammatory cytokines; it also summarizes clinical studies on progestogen supplementation. These studies lend credibility to the proposal that progestogens should be explored for the immunotherapeutic management of pregnancy complications.

1. Introduction

A fact that is not appreciated by most laypersons, and even by doctors who are not in the field of obstetrics and gynaecology, is that pregnancy is not nearly as successful as one might assume. Numerous potential complications may arise between the long period of gestation from conception to delivery; these include threatened abortion, spontaneous miscarriage, pre-eclampsia, preterm rupture of membranes and preterm labour and delivery. As much as 30% of pregnancies result in miscarriage within two weeks of fertilization and another 15–20% of conceptions fail within 14 weeks of gestation.[1]

Numerous studies have elucidated the roles of the maternal immune system in contributing to the pathogenesis of conditions such as spontaneous miscarriage, pre-eclampsia and pre-term delivery; however, this article will focus only on the immunology of spontaneous miscarriage.

2. Spontaneous miscarriage

Spontaneous miscarriage, defined as a clinically detectable pregnancy loss prior to 20 weeks of gestation, occurs in one out of every four pregnant women. Recurrent spontaneous miscarriage (RSM) is defined as the occurrence of three or more pregnancy losses before the 20th week of gestation and is one of the most challenging complications of pregnancy. Interestingly, despite years of research, only about 40–50% of the cases of RSM are attributable to the so called "known" causes such as chromosomal anomalies, endocrinologic abnormalities, infections, anatomic problems and humoral factors, and as much as 60% consigned conveniently (and inevitably) to the mysterious "black box" designated as "unknown" or "unexplained" aetiology (Fig. 1).[1–3] Thus, the causes of RSM remain "unexplained" in the majority of women; the fact that the aetiology is unexplained in such a large proportion of cases of RSM has inspired the exploration of possible immunologic etiologies of RSM. As is true for many fields such as rheumatology, nephrology, and pulmonology, immunologists have been very active in field of obstetrics and gynaecology, ascertaining whether immunologic factors are responsible for complications

E-mail address: raj@hsc.edu.kw.

http://dx.doi.org/10.1016/j.cmrp.2016.10.008

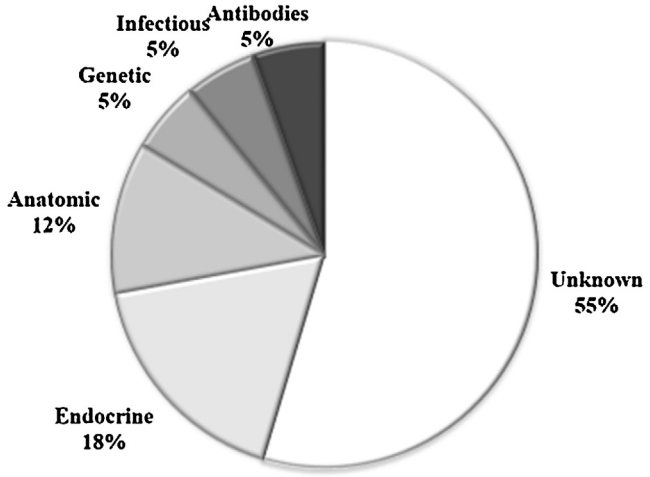

Fig. 1. Causes of recurrent spontaneous miscarriage.
Source: Adapted from Refs.[1–3]

which are unexplained in terms of genetic, infectious and endocrinologic factors.

3. Immune etiologic factors in recurrent spontaneous miscarriage

While humoral and cell-mediated etiologic factors have been investigated, interestingly the conceptus appears to be resistant to attack by humoral immunity except for anti-phospholipid antibodies which are clearly implicated in a proportion of RSM.[4] Anti-phospholipid antibodies appear to cause pregnancy loss by interfering with the anti-thrombotic role of phospholipids.

This naturally led to a great deal of attention being focused on the possibility of cell-mediated immune effectors as possible etiologic factors, including the study of maternal T lymphocytes, macrophages and natural killer (NK) cells both in maternal peripheral blood and in uteroplacental tissues. An excellent framework for delineating how the immune system influences and regulates responses to different types of antigenic stimuli and different kinds of pathogens emerged from the revolutionary discovery of the different subsets of T helper lymphocytes and the cytokines produced by them.

3.1. Cytokines

What is the relevance of cytokines to pregnancy and to pregnancy loss? What are cytokines anyway? Cytokines are among the most critical molecules of the immune system, playing extremely important roles as communication signals between cells of the immune system primarily, but also between cells of other systems of the body. Cytokines are powerful, versatile, multipotent mediators of an impressive range of reactions ranging from the induction of normal immune responses, rejection of allografts, autoimmune diseases and hypersensitivity.[5,6]

Cytokines synthesized and secreted by immune cells such as macrophages, NK cells and in particular, T helper (Th) cells, have received a great deal of attention from researchers in the field of maternal–foetal immunology. Th1 and Th2 cells are the principal subsets of T helper cells; they have different patterns of cytokine production and thus different roles in immune responses.[7,8] Th1 cells secrete the cytokines interferon (IFN) γ, tumour necrosis factor (TNF) β, TNFα and interleukin (IL)-2; these Th1-type cytokines activate and sustain robust cell-mediated and inflammatory reactions such as cytotoxicity and delayed-type hypersensitivity; as such these inflammatory cytokines are implicated in graft rejection, autoimmune disease pathology and inflammatory tissue damage. Th2 cells, on the other hand, secrete the cytokines IL-4, IL-5, IL-6, IL-10 and IL-13 which encourage vigorous antibody production. Th1 and Th2 cells are mutually opposed to each other; an individual who produces a strong Th1 response generally tends to have a low Th2 response and vice versa.

3.2. Cytokines and pregnancy loss

Interestingly enough, pregnancy seems to bring about an enhancement in humoral immune responses and a decrease in cell-mediated immune reactivity; moreover, the severity of cell-mediated autoimmune disorders tend to be down-regulated.[9] This "natural pregnancy-induced immunomodulation" is consistent with a downregulation of Th1 responses and upregulation of Th2 responses.[10,11] In fact, the activation of some forms of maternal cellular immunity is potentially injurious to foetal development. Cellular immunity mediated by effector cells and/or cytokines released by them have been shown to harmful to the conceptus. The administration of the Th1-type inflammatory cytokines TNFα, IFNγ and IL-2 into pregnant mice causes abortions while the injection of anti-TNFα antibodies brings reduced abortion rates in a murine model of natural, immunologically-mediated abortion.[12] TNFα and IFNγ restrain the outgrowth of human trophoblast cells *in vitro*[13] and synergistically stimulate the apoptotic killing of human primary villous trophoblast cells.[14] We have demonstrated that the stimulation of maternal spleen cells in vitro with placentas of mice prone to immunologically-mediated spontaneous foetal resorption results in the secretion of high levels of TNFα, IFNγ and IL-2[15]; it should be emphasized that these cytokines together fit the profile of Th1 or pro-inflammatory cytokines.

Given that pro-inflammatory cytokines have so many cytotoxic and tissue-damaging capabilities, it is not surprising that women with recurrent spontaneous miscarriage have a greater bias towards a Th1-type or pro-inflammatory cytokine profile as compared to women with healthy pregnancy.[16] Hill et al. showed that peripheral blood cells from women with a history of RSM when stimulated with human trophoblast antigens produce higher levels of Th1 cytokines with embryotoxic activity.[17] We have demonstrated the production of significantly higher levels of the anti-inflammatory Th2 cytokines IL-4, IL-5 and IL-10 by mitogen-stimulated peripheral lymphocytes from women with a history of normal pregnancy, and conversely, elevated levels of the pro-inflammatory cytokines IL-2, IFNγ and TNFα by women with a history of healthy pregnancies.[18,19] This was corroborated by our studies on maternal immune reactivity to placental antigens stimulated either by co-culturing maternal lymphocytes with autologous placental cells or by exposing maternal lymphocytes to a trophoblast antigen preparation.[20] Th1 or pro-inflammatory cytokine dominance in RSM as opposed to a stronger Th2-bias in healthy pregnancy was supported by our observation that ratios of inflammatory cytokines to anti-inflammatory cytokines were higher in the RSM group as compared to the healthy pregnancy group. Piccinni et al. reported lower levels of Th2 cytokine-producing T cell clones from the decidua of women with unexplained RSM than from women with normal pregnancy.[21] An interesting study by Clerici et al. showed decreased production of the anti-inflammatory cytokines IL-4 and IL-10 and increased production of the pro-inflammatory cytokines IFNγ and IL-2 by antigen-stimulated lymphocytes from women with RSM as opposed to those from normal pregnancy even 1–2 weeks before any upcoming pathology could be detected.[22]