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CUTTING EDGE IN AUTOIMMUNITY

Interdisciplinary exchange of ideas: progestagens for autoimmunity, biologics for pregnancy complications

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Abstract In recent years, there has been a growing interest in the role of immune, alloimmune and autoimmune processes in the pathogenesis of spontaneous preterm birth and recurrent pregnancy loss. The association between an inflammatory response and preterm labor has been established. Indeed, many women suffering from preterm labor have elevated inflammatory markers such as tumor necrosis factor alpha, interleukin 6 and matrix metaloproeinase 8. The role of immune processes in the pathogenesis of recurrent pregnancy loss has also been widely researched. Progesterone induces many physiologic effects necessary for healthy pregnancy, and progestagens supplementation has been used as an approach to prevent preterm labor and recurrent pregnancy loss. Progestagens also have potent anti-inflammatory and immunomodulatory actions. Because preterm labor and recurrent pregnancy loss are associated with abnormal inflammation, progestagens may maintain healthy pregnancy through both endocrine and immunologic actions. These immunologic actions, such as suppression of Th1- and Th17-related responses, enhancement of regulatory T cell (Tregs) activity and suppression of inflammation, may also be involved in pregnancy-induced remission of certain autoimmune diseases such as rheumatoid arthritis (RA) and multiple sclerosis (MS). Accordingly, there is growing interest in the potential therapeutic role of progestagens in the treatment of MS and RA. In this review, we suggest that biologic autoimmune modulators, especially those which affect immune pathways similar to progestagens, may provide more potent and specific effects, and hence better results than progestagens, in preventing preterm labor and recurrent pregnancy loss.

Keywords Progesterone · Immunomodulation · Preterm labor · Recurrent pregnancy loss · Biologics · T cells

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Introduction

In recent years, there has been growing interest in the role of immune, alloimmune and autoimmune processes in the pathogenesis of spontaneous preterm birth and recurrent pregnancy loss (RPL).

Significant evidence has accumulated regarding the role of intrauterine inflammation in preterm labor, especially when it occurs early in gestation [1]. Women with preterm labor often have elevated blood inflammatory markers such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) or matrix metaloproeinase 8 (MMP-8). The association of elevated maternal blood inflammatory markers with preterm labor appears to be independent of intra-amniotic

inflammation [2]. This suggests that maternal immune responses rather than infection of the conceptus are important drivers of inflammation-associated preterm birth. This hypothesis is supported by recent data showing significant correlations between maternal IL-6, TNF-α and other inflammatory gene polymorphisms and risk of spontaneous preterm birth [3]. Moreover, in a systemic review including 17 primary studies compromising 6,270 participants, IL-6 in cervicovaginal fluid and IL-6 and C-reactive protein (CRP) in amniotic fluid were predictive of spontaneous preterm birth in asymptomatic women [4].

RPL is associated with certain autoimmune diseases (ADs), most notably the antiphospholipid syndrome (APS), for which RPL is a diagnostic criterion [5]. Again, this suggests that abnormalities in the maternal immune response negatively impact pregnancy outcomes. However, the mechanisms linking AD to RPL remain obscure.

Progesterone for preterm labor

Progesterone (pregn-4ene-3, 20-dione) is a steroid hormone that is critical for maintenance of early pregnancy; in the first 7–9 weeks of gestation, it is produced by the corpus luteum. Its name is based on this function—progestational steroidal ketone. Before 7 weeks of gestation, surgical removal of the corpus luteum or administration of a progesterone antagonist will result in abortion [6, 7]. After 7–9 weeks of gestation, the placenta assumes progesterone production, and there is a gradual increase in serum levels throughout pregnancy, reaching levels that are up to 5,000 times higher at term than those in non-pregnant women [8].

There is also compelling evidence that progestagens supplementation may help prevent preterm birth in women who have suffered from a previous spontaneous preterm singleton birth and in women with a short cervix on ultrasound examination in the current pregnancy [9, 10].

The mechanism by which progestagens delay or prevent preterm births is less clear. The classic theory was that progestagens delay preterm birth in these women by maintaining uterine muscle (myometrium) quiescence—that is, preventing premature contractions that could lead to further shortening and even dilatation of the cervix. Progestagens act to maintain uterine quiescence by inhibiting the expression in myometrial cells of genes whose downstream products are involved in uterine contraction, e.g., prostaglandins, oxytocin receptors and gap junction proteins [11, 12]. However, there is a growing understanding that progestagens ability to prevent preterm labor involves their immunomodulatory and anti-inflammatory actions [13].

Progestagens for recurrent pregnancy loss

Another indication for progestagen therapy in obstetrics is RPL, especially in unexplained RPL. A meta-analysis of four trials, including 225 women suffering from RPL, showed that progestagen supplementation significantly decreased the miscarriage rate compared to placebo or no treatment [14]. However, all the trials included in the meta-analysis used synthetic progestagens rather than progesterone itself. Moreover, methodologic limitations of these trials mean that additional trials are required. There is currently an ongoing trial of micronized progesterone for the treatment of RPL—the PROMISE study (ISRCTN 92644181), results of which are eagerly awaited. The ability of progestagen supplementation to prevent RPL is believed to arise from both the hormone's effect on the uterus leading to successful implantation [14] and immune modulation [15, 16].

Progestagens and immunity

Progestagens have many immunomodulatory effects, which are mainly immunosuppressive. These effects are achieved through direct actions on cells of both the innate and adaptive immune systems.

In the adaptive immune system, leukocytes express specific nuclear and membrane progesterone receptors [17], and progestagens have effects in both B cells and T cells. Important effects appear to be mediated through T helper (Th) cells. High levels of progesterone, such as those found in pregnancy, suppress the development and functions of Th1 and Th17 cells while inducing the function and development of Th2 and Treg cells [17, 18]. This shift toward increased Treg/Th2 activity and reduced Th1/Th17 is possibly involved in the remission of multiple sclerosis (MS) and rheumatoid arthritis (RA) during pregnancy and could also explain the increased susceptibility of pregnant women to infection by intracellular pathogens such as *Listeria monocytogenes*, HSV-2 and HIV [19–21].

Progestagens may also dampen humoral immunity by suppressing immunoglobulin class switch recombination in B cells—a process required for B cells to manufacture highly active antibodies (Abs), either protective or self-reactive (autoimmune) [22]. During pregnancy, progesterone and other pregnancy hormones alter posttranslational glycosylation of autoAbs, rendering them less capable of inducing inflammation [23, 24]. Progestagens have additional effects on components of the innate immune system. Progestagens can program dendritic cells (DCs) that favor the differentiation of Treg cells and not Th1 or Th17 cells [25]. Progestagens also suppresses the production of several pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 IL-8 and IL-23 [13, 26].

Due to the increasing recognition of progestagens' immunomodulatory effects and their potential roles in remission of RA and MS during pregnancy, it has been postulated that progestagens may have a therapeutic potential for these ADs, in both sexes and outside of pregnancy. A clinical trial is presently being performed to examine the potential benefit of progestagens for the treatment and prevention of MS relapses [27].

Biologics for prevention of recurrent pregnancy loss and preterm birth

Improved understanding of the pathophysiology underlying RA has led to the development of targeted treatments, termed biologic disease modifying anti-rheumatic drugs (bDMARDs). In the case of RA, the main biologic treatment approaches achieving good clinical impact are blockade of the inflammatory cytokines TNF-α, IL-1β or IL-6, B cell depletion and disruption of T cell co-stimulation. We postulate that some of these biologic treatments could, like progestagens, help prevent preterm labor and RPL.

In the case of preterm labor, both TNF-α and IL-6 have been reported to be involved in preterm birth caused by inflammatory processes [1], and their inhibition may lead to better results in preventing preterm labor.

TNF-α inhibitors were the first approved bDMARDs and for patients with persistently active RA; the combination of TNF-α inhibitors and methotrexate has proven to be safe, well tolerated and effective therapy [28]. Tocilizumab is a humanized antihuman IL-6 receptor antibody with proven therapeutic effect in patients with RA when administered parenterally [29, 30]. The drug may cause dyslipidemia but is generally well tolerated [31].

Of these drugs, TNF-α inhibitors have been the most extensively studied in pregnancy. TNF-α inhibitors have been classified by the FDA as pregnancy Category B drugs, meaning that animal reproduction studies have not shown any risk to the fetus, but there are no adequate and well-controlled studies in human pregnancy. TNF-α inhibitors like all the biologics are IgG molecules (either completely or partially). Fetal exposure to IgG is very low during organogenesis, but placental transfer starts at the beginning of the second trimester and increases until term. The biologics do not seem to be teratogenic but do increase the risk of infection after birth when given in late pregnancy [32]. Therefore, there may be some barriers to future investigation into possible role for biologics in the prevention of preterm labor.

In the case of RPL, the possible benefit of immunotherapy has been widely assessed. In a Cochrane review including 20 trials involving paternal cell immunization, trophoblast membranes transfusion, third party donor leukocytes and intravenous immune globulin and immunotherapy provided no significant beneficial effect over placebo in improving the live birth rate when all patients with two or more miscarriages were analyzed as one homogeneous group [33]. However, subgroup analysis has shown that immunomodulation, whether paternal leukocyte immunization [34, 35] or intravenous immunoglobulin treatment [36], may be highly effective on certain subgroups of patients.

In RPL, approximately 40 % of miscarriages are due to embryonic aneuploidy. Immunotherapy cannot prevent aneuploid embryos from being lost. Hence, further research is required focusing on the possible benefit of specific biologics in the prevention of RPL with chromosomally normal embryos. This hypothesis is strengthened by a recent study conducted on women suffering from RPL and increased peripheral NK-cell number and/or activity. This study showed that etanercept (a TNF-α blocker) immunotherapy significantly decreased NK-cell activity. This effect was significantly higher in women with subsequent pregnancy success, but not in those with pregnancy failure [37]. Additionally, work with the Th-2 cytokine G-CSF has shown promising results in RPL [38].

Summary

It has been 37 years since Siiteri first named progestagens as nature's immunosuppressants [39]. We believe that better understanding of the immunomodulatory actions of progesterone during healthy pregnancy could identify inflammatory pathways in PTL and PRL that would be amenable to therapeutic targeting by existing immunomodulatory drugs.

Conflict of interest The authors declare that they have no conflict of interests.

References

1. Combs CA, Gravett M, Garite TJ, Hickok DE, Lapidus J, Porreco R, et al. Amniotic fluid infection, inflammation, and colonization in preterm labor with intact membranes. Am J Obstet Gynecol. 2014;210(2):125.e1–15. doi:10.1016/j.ajog.2013.11.032.
2. Kim SM, Romero R, Lee J, Mi Lee S, Park CW, Shin Park J, et al. The frequency and clinical significance of intra-amniotic inflammation in women with preterm uterine contractility but without cervical change: Do the diagnostic criteria for preterm labor need to be changed? J Matern Fetal Neonatal Med. 2012;25(8):1212–21. doi:10.3109/14767058.2011.629256.
3. Moura E, Mattar R, de Souza E, Torloni MR, Gonçalves-Primo A, Daher S. Inflammatory cytokine gene polymorphisms and spontaneous preterm birth. J Reprod Immunol. 2009;80(1–2):115–21. doi:10.1016/j.jri.2008.11.007.
4. Wei SQ, Fraser W, Luo ZC. Inflammatory cytokines and spontaneous preterm birth in asymptomatic women: a systematic review. Obstet Gynecol. 2010;116(2 Pt 1):393–401. doi:10.1097/AOG.0b013e3181e6dbc0.

5. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4(2):295–306. doi:10.1111/j.1538-7836.2006.01753.x.
6. Csapo AI, Pulkkinen M. Indispensability of the human corpus luteum in the maintenance of early pregnancy luteectomy evidence. Obstet Gynecol Surv. 1978;33(2):69–81.
7. Peyron R, Aubény E, Targosz V, Silvestre L, Renault M, Elkik F, et al. Early termination of pregnancy with mifepristone (RU 486) and the orally active prostaglandin misoprostol. N Engl J Med. 1993;328(21):1509–13. doi:10.1056/NEJM199305273282101.
8. Cunningham FG, Leveno KJ, Bloom SL, Spong CY, S. DJ, Hoffman BL et al. Placentation, embryogenesis, and fetal development. In: Cunningham FG, Leveno KJ, Bloom SL, Spong CY, S. DJ, Hoffman BL et al., editors. Willimas obstetrics. 24th ed. New York: McGraw-Hill Education/Medical; 2014. p. 106–15.
9. Committee on Practice Bulletins—Obstetrics. TeACoOaG. Practice bulletin no. 130: prediction and prevention of preterm birth. Obstet Gynecol. 2012;120(4):964–73. doi:10.1097/AOG.0b013e3182723b1b.
10. Romero R, Nicolaides K, Conde-Agudelo A, Tabor A, O'Brien JM, Cetingoz E, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. Am J Obstet Gynecol. 2012;206(2):124.e1–19. doi:10.1016/j.ajog.2011.12.003.
11. Norwitz ER, Robinson JN, Challis JR. The control of labor. N Engl J Med. 1999;341(9):660–6. doi:10.1056/NEJM199908263410906.
12. Challis JRG, Matthews SG, Gibb W, Lye SJ. Endocrine and paracrine regulation of birth at term and preterm. Endocr Rev. 2000;21(5):514–50. doi:10.1210/edrv.21.5.0407.
13. Okabe H, Makino S, Kato K, Matsuoka K, Seki H, Takeda S. The effect of progesterone on genes involved in preterm labor. J Reprod Immunol. 2014;. doi:10.1016/j.jri.2014.03.008.
14. Haas DM, Ramsey PS. Progestogen for preventing miscarriage. Cochrane Database Syst Rev. 2013;10:CD003511. doi:10.1002/14651858.CD003511.pub3.
15. Kwak-Kim J, Bao S, Lee SK, Kim JW, Gilman-Sachs A. Immunological modes of pregnancy loss: inflammation, immune effectors, and stress. Am J Reprod Immunol. 2014;. doi:10.1111/aji.12234.
16. Choi BC, Polgar K, Xiao L, Hill JA. Progesterone inhibits in vitro embryotoxic Th1 cytokine production to trophoblast in women with recurrent pregnancy loss. Hum Reprod. 2000;15(Suppl. 1):46–59.
17. Hughes GC. Progesterone and autoimmune disease. Autoimmun Rev. 2012;11(6–7):A502–14. doi:10.1016/j.autrev.2011.12.003.
18. Arck PC, Hecher K. Fetomaternal immune cross-talk and its consequences for maternal and offspring's health. Nat Med. 2013;19(5):548–56. doi:10.1038/nm.3160.
19. Kaushic C, Roth KL, Anipindi V, Xiu F. Increased prevalence of sexually transmitted viral infections in women: the role of female sex hormones in regulating susceptibility and immune responses. J Reprod Immunol. 2011;88(2):204–9. doi:10.1016/j.jri.2010.12.004.
20. Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. N Engl J Med. 2014;370(23):2211–8. doi:10.1056/NEJMra1213566.
21. Rowe JH, Ertelt JM, Aguilera MN, Farrar MA, Way SS. Foxp3(+) regulatory T cell expansion required for sustaining pregnancy compromises host defense against prenatal bacterial pathogens. Cell Host Microbe. 2011;10(1):54–64. doi:10.1016/j.chom.2011.06.005.
22. Sakiani S, Olsen NJ, Kovacs WJ. Gonadal steroids and humoral immunity. Nat Rev Endocrinol. 2013;9(1):56–62. doi:10.1038/nrendo.2012.206.
23. Arnold JN, Wormald MR, Sim RB, Rudd PM, Dwek RA. The impact of glycosylation on the biological function and structure of human immunoglobulins. Annu Rev Immunol. 2007;25:21–50. doi:10.1146/annurev.immunol.25.022106.141702.
24. Prados MB, La Blunda J, Szekeres-Bartho J, Caramelo J, Miranda S. Progesterone induces a switch in oligosaccharyltransferase isoform expression: consequences on IgG N-glycosylation. Immunol Lett. 2011;137(1–2):28–37. doi:10.1016/j.imlet.2011.01.017.
25. Hughes GC, Clark EA. Regulation of dendritic cells by female sex steroids: relevance to immunity and autoimmunity. Autoimmunity. 2007;40:470–81.
26. Ostensen M, Villiger PM. The remission of rheumatoid arthritis during pregnancy. Semin Immunopathol. 2007;29(2):185–91. doi:10.1007/s00281-007-0072-5.
27. Vukusic S, Ionescu I, El-Etr M, Schumacher M, Baulieu EE, Cornu C, et al. The Prevention of Post-Partum Relapses with Progestin and Estradiol in Multiple Sclerosis (POPART'MUS) trial: rationale, objectives and state of advancement. J Neurol Sci. 2009;286(1–2):114–8. doi:10.1016/j.jns.2009.08.056.
28. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med. 1999;340(4):253–9. doi:10.1056/NEJM199901283400401.
29. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008;371(9617):987–97. doi:10.1016/S0140-6736(08)60453-5.
30. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis. 2010;69(1):88–96. doi:10.1136/ard.2008.105197.
31. Singh JA, Beg S, Lopez-Olivo MA. Tocilizumab for rheumatoid arthritis: a Cochrane systematic review. J Rheumatol. 2011;38(1):10–20. doi:10.3899/jrheum.100717.
32. Ostensen M. Safety issues of biologics in pregnant patients with rheumatic diseases. Ann N Y Acad Sci. 2014;1317(1):32–8. doi:10.1111/nyas.12456.
33. Porter TF, LaCoursiere Y, Scott JR. Immunotherapy for recurrent miscarriage. Cochrane Database Syst Rev. 2006;2:CD000112. doi:10.1002/14651858.CD000112.pub2.
34. Carp HJ, Toder V, Torchinsky A, Portuguese S, Lipitz S, Gazit E, et al. Allogenic leukocyte immunization after five or more miscarriages. Recurrent Miscarriage Immunotherapy Trialists Group. Hum Reprod. 1997;12(2):250–5.
35. Daya S, Gunby J. The effectiveness of allogeneic leukocyte immunization in unexplained primary recurrent spontaneous abortion. Recurrent Miscarriage Immunotherapy Trialists Group. Am J Reprod Immunol. 1994;32(4):294–302.
36. Hutton B, Sharma R, Fergusson D, Tinmouth A, Hebert P, Jamieson J, et al. Use of intravenous immunoglobulin for treatment of recurrent miscarriage: a systematic review. BJOG. 2007;114(2):134–42. doi:10.1111/j.1471-0528.2006.01201.x.
37. Jerzak M, Ohams M, Górski A, Baranowski W. Etanercept immunotherapy in women with a history of recurrent reproductive failure. Ginekol Pol. 2012;83(4):260–4.
38. Scarpellini F, Sbracia M. Use of granulocyte colony-stimulating factor for the treatment of unexplained recurrent miscarriage: a randomised controlled trial. Hum Reprod. 2009;24(11):2703–8. doi:10.1093/humrep/dep240.
39. Siiteri PK, Febres F, Clemens LE, Chang RJ, Gondos B, Stites D. Progesterone and maintenance of pregnancy: Is progesterone nature's immunosuppressant? Ann N Y Acad Sci. 1977;286:384–97.