Maternal-fetal conflict in intraamniotic infection

R. Romero [1] *, L. Yeo [1, 2], J. Miranda [1, 2], T. Chaiworapongsa [1, 2]
(Detroit, Michigan, USA)

Abstract

Aim: to examine the biological consequences of intraamniotic infection in pregnancy in the context of the maternal-fetal conflict relationship.

Materials and methods: review of the literature including the frequency of microbial invasion of the amniotic cavity, intraamniotic inflammation, fetal systemic inflammation, neonatal outcome, and the physiological adaptations of the immune system during pregnancy.

Results: 1) intraamniotic infection is causally linked to the onset of preterm labor and preterm premature rupture of membranes; 2) diagnosis of intraamniotic infection requires at this time amniocentesis for studies of amniotic fluid, and the use of cultivation and molecular techniques to identify microorganisms and tailor therapy; 3) micro-organisms may invade the human fetus and cause a systemic inflammatory response

1 - Perinatology Research Branch - NICHD/NIH/DHHS - Bethesda, Maryland and Detroit, Michigan - 3990 John R - Box 4 - Detroit, Michigan 48201 - USA
2 - Wayne State University School of Medicine - Department of Obstetrics and Gynecology - Hutzel Women's Hospital - 3990 John R - Box 4 - Detroit, Michigan 48201 - USA

* Correspondence to: prbchiefstaff@med.wayne.edu

syndrome which may cause damage to multiple organ systems, including the brain; 4) treatment of intraamniotic infection may require induction of labor which can create the conditions for maternal-fetal conflict of interest; 5) treatment with antibiotic administration is possible, and has been reported in a selected group of patients.

Conclusions: we propose that the onset of preterm labor in the context of intraamniotic infection has survival value for the mother. However, when this occurs close to term, the onset of labor may benefit both hosts. Balancing the interests of both mother and fetus in early gestations is challenging because this condition represents a diagnostic and therapeutic challenge.

Keywords: preterm labor, intraamniotic infection, survival value, evolution, reproductive fitness

Public declaration of interest

The authors declare that they do not have direct or indirect interest (financial or in kind) with a private organization, industrial or commercial in connection with the subject presented.

INTRODUCTION

Microorganisms have been the most powerful force shaping the immune system throughout evolution. Defense against infection is an essential function of most living matter. It can be argued that the primary function of the immune system is protection of the host against micro- and macroparasites. The functioning of this system is easy to envision in a simple organism such as an amoeba. The emergence of viviparity imposed a major challenge to the immune system over that of oviparous species.

Viviparity requires the tolerance of the semi-allograft. The mechanisms responsible for the tolerogenic state of pregnancy have been subject of investigation for decades. In general terms, it is

proposed that this is accomplished by down regulating the adaptive or specific immune response to tolerate the allograft [1], and activation of the innate immune response to protect the host against infection. Indeed, there is strong evidence for the activation of the cellular and soluble components of the innate immune system. For example, there is evidence of activation of granulocytes and monocytes in the peripheral blood of pregnant women [2, 3]. They also have high concentrations of acute phase reactant proteins [4-6], such as fibrinogen, C-reactive protein, etc. This activation is proposed to protect the mother against invading microorganisms.

This physiologic adaptation of pregnancy may have adverse consequences when the activation evolves into a cytokine storm. This has been the explanation for the increased death of pregnant women in response to viral and bacterial infections. This was originally observed in the influenza pandemic of 1918 and recently was witnessed in the H1N1 epidemic of 2009 [7, 8]. Pregnant women also are more prone to develop adult respiratory distress syndrome during the course of systemic infections such as pyelonephritis [9], when compared to non-pregnant women. Experimental evidence that confirms this is that the Shwartzman reaction requires two injections of endotoxin in non-pregnant animals [a sensitizing injection and a triggering one], while pregnant animals develop the Shwartzman reaction after only one dose of endotoxin [10]. This has been attributed to the baseline state of activation of the innate immune system and the molecular mechanisms proposed to be responsible involved increased production of interleukin 12 [IL-12] which can prime the innate immune system [1].

The fetal immune system has a complex developmental stage. Ontogeny recapitulates phylogeny and the innate immune system develops before the adaptive system. As pregnancy progresses, there is an intensive dialogue occurring between the immune systems of the mother and fetus and bidirectional exchange of cellular and soluble components. This includes cell-free DNA and RNA. Microchimerism has been implicated in the genesis of delay autoimmune disorders (e.g. systemic sclerosis) [11].

Despite the intimacy of contact between mother and fetus in eutherian mammals, and especially those with a hemochorial placentation, maternal anti-fetal rejection is a relatively rare phenomenon. This has been observed in cases of late preterm birth [12] (lesions of chronic chorioamnionitis and chronic villitis), and fetal death [13].

Although the maternal-fetal conflict theory has been invoked to explain imprinting [14] and the development of some disorders such as

preeclampsia [15, 16], we believe that the success of pregnancy is due to a cooperative relationship between fetus and mother, despite their different genetic makeup. Yet, insults may disrupt this cooperative relationship and create conditions for conflict. Intrauterine infection is an interesting model in which to explore the maternal-fetal conflict that can arise and how such infections are handled to maintain reproductive fitness.

I. INTRAAMNIOTIC INFECTION

The conventional paradigm is that the amniotic cavity is sterile for bacteria. There is abundant evidence derived from cultivation [17, 18], as well as molecular microbiologic techniques [19, 20], that most pregnancies do not have bacteria in the amniotic cavity. The case for viruses has been less adequately studied, but the advent of next generation sequencing [21, 22] should resolve the question of whether viruses are normally present in the amniotic cavity. The current tenet is that the neonate acquires its microbiome during the course of parturition and under physiologic conditions by passage through the birth canal [23, 24].

Intraamniotic infection has been identified in cases of preterm labor with intact membranes [25], preterm premature rupture of membranes [26], a short cervix [27-29], placenta previa [30], fetal death [31-34], and other conditions. These infections are causally linked to the onset of preterm labor and premature rupture of membranes. Microorganisms present in the amniotic cavity can elicit an intraamniotic inflammatory response and if this is not enough to signal the onset of labor, fetal invasion may occur with the development of a fetal inflammatory response syndrome (FIRS) [35-37] and multi-organ involvement [38-42], ranging from a dermatitis [43] to neuro-inflammation [44-46] which may predispose to cerebral palsy [47-49].

Microbial invasion of the amniotic cavity (MIAC) poses a challenge to the fetal immune system. Antimicrobial peptides normally present in the amniotic cavity (e.g. defensins, lactoferrin, calprotectin, etc.) [50] may control the proliferation of bacteria. However, a cellular immune response primarily composed of neutrophils can participate in the control of infection. Yet, this inflammatory process may signal the onset of labor. Inflammation at the level of the maternal-fetal interface can activate the decidua, myometrium and induce cervical ripening.

II. MATERNAL-FETAL CONFLICT AND PRETERM PARTURITION

Parturition can be considered a unique mechanism of host defense which is capable of ridding the mother of invading microorganisms and infected tissue. Yet, resorting to this mechanism sets the stage for maternal-fetal conflict.

When intraamniotic infections occur at term, or when the fetus has attained maturity, the onset of parturition has survival value for the host, mother, and fetus. On the other hand, when the intraamniotic infection occurs early in pregnancy (e.g. 24 weeks of gestation), resorting to the onset of preterm parturition is a condition that would be lethal to the fetus before the development of modern neonatal intensive care units. It can be argued that the onset of preterm labor in the context of infection has primarily survival value for the mother, as she is capable of dramatically minimizing the burden of infection (by expelling the membranes, placenta, and amniotic fluid) and maintaining her reproductive capacity (reproductive fitness).

When intraamniotic infection occurs before term, but when the fetus has achieved near maturity (i.e. 34 weeks of gestation), the onset of labor may have survival value for both mother and fetus. There is evidence that inflammatory mediators, such as interleukin 1 (IL-1) can induce the production of surfactant [51-53], and this phenomenon has been invoked to explain the lower rate of respiratory distress syndrome in some cases of histologic chorioamnionitis [54].

This adaptive interpretation of the onset of preterm labor in the context of infection is buttressed by the observation that the molecular machinery responsible for the onset of preterm labor in infection is the same one used by non-pregnant hosts to deal with infection. There is compelling evidence that pro-inflammatory cytokines, such as IL-1 [55], tumor necrosis factor alpha [56], and other mediators generated during the course of acute inflammation [e.g. prostaglandins [57, 58] can induce the onset of labor in pregnant animals. The evidence is strong for the participation of the same systems in the onset of preterm labor in mammalian species, including the human.

There is evidence that the fetus plays a role in the onset of parturition in the sheep, and a similar role has been attributed to the human fetus in preterm labor [59, 60]. Indeed, among fetuses with preterm premature rupture of membranes, those with FIRS are more likely to go into labor than those who do not have fetal inflammation [35]. The relative benefits of preterm parturition for mother and fetus

are a function of gestational age and the degree to which fetal systemic inflammation may have caused organ damage to the conceptus. In extreme circumstances, an intraamniotic and fetal systemic inflammatory response would lead to the onset of premature labor at a very early gestation (i.e. 22 weeks). Under these circumstances, preterm labor could be interpreted as a unique response in nature in which one host (the fetus) risks survival and thus maintaining reproductive fitness for the mother. This would be a novel application of kin selection theory during pregnancy.

The optimal management of intraamniotic infection during pregnancy requires diagnosis. It is now clear that maternal symptoms and signs are insensitive indicators of MIAC and therefore, amniocentesis is (for now) required to diagnose this condition. When infection is diagnosed close to term, induction of labor has been recommended to maximize a favorable outcome for both patients. In preterm gestations, the options range from antibiotic administration to eradicate intraamniotic infection (followed by careful monitoring) to induction of labor. Gestational age and the presence of fetal lung maturity are critical parameters in determining when induction should be undertaken.

CONCLUSION

We propose that the onset of preterm labor in the context of intraamniotic infection has survival value for the mother. However, when this occurs close to term, the onset of labor may benefit both hosts. Balancing the interests of both mother and fetus in early gestations is challenging because this condition represents a diagnostic and therapeutic challenge.

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Bibliography

[1] Sacks G, Sargent I, Redman C. An innate view of human pregnancy. Immunol Today 1999 Mar;20(3):114-8.

[2] Luppi P, Haluszczak C, Betters D, Richard CA, Trucco M, DeLoia JA. Monocytes are progressively activated in the circulation of pregnant women. J Leukoc Biol 2002 Nov;72(5): 874-84.

[3] Naccasha N, Gervasi MT, Chaiworapongsa T, Berman S, Yoon BH, Maymon E *et al.* Phenotypic and metabolic characteristics of monocytes and granulocytes in normal pregnancy and maternal infection. Am J Obstet Gynecol 2001 Nov;185(5):1118-23.

[4] Stirling Y, Woolf L, North WR, Seghatchian MJ, Meade TW. Haemostasis in normal pregnancy. Thromb Haemost 1984 Oct 31;52(2):176-82.

[5] Comeglio P, Fedi S, Liotta AA, Cellai AP, Chiarantini E, Prisco D *et al.* Blood clotting activation during normal pregnancy. Thromb Res 1996 Nov 1;84(3):199-202.

[6] Richani K, Soto E, Romero R, Espinoza J, Chaiworapongsa T, Nien JK *et al.* Normal pregnancy is characterized by systemic activation of the complement system. J Matern Fetal Neonatal Med 2005 Apr;17(4):239-45.

[7] Lim BH, Mahmood TA. Influenza A H1N1 2009 (Swine Flu) and Pregnancy. J Obstet Gynaecol India 2011 Aug;61(4):386-93.

[8] Liu SL, Wang J, Yang XH, Chen J, Huang RJ, Ruan B *et al.* Pandemic influenza A(H1N1) 2009 virus in pregnancy. Rev Med Virol 2012 Mar 13. doi: 10.1002/rmv.1712 (sous presse).

[9] Gurman G, Schlaeffer F, Kopernic G. Adult respiratory distress syndrome as a complication of acute pyelonephritis during pregnancy. Eur J Obstet Gynecol Reprod Biol 1990 Jul-Aug;36(1-2):75-80.

[10] Mori W. The Shwartzman reaction: a review including clinical manifestations and proposal for a univisceral or single organ third type. Histopathology 1981 Mar;5(2):113-26.

[11] Parant O, Khosrotehrani K, Aractingi S. (Gestational microchimerism in human diseases). Presse Med 2009 Apr;38(4):584-90.

[12] Kim CJ, Romero R, Kusanovic JP, Yoo W, Dong Z, Topping V *et al.* The frequency, clinical significance, and pathological features of chronic chorioamnionitis: a lesion associated with spontaneous preterm birth. Mod Pathol 2010 Jul;23(7):1000-11.

[13] Lee J, Romero R, Dong Z, Xu Y, Qureshi F, Jacques S *et al.* Unexplained fetal death has a biological signature of maternal anti-fetal rejection: chronic chorioamnionitis and allo-immune anti-human leucocyte antigen antibodies. Histopathology 2011 Nov;59(5):928-38.

[14] Wolf JB, Hager R. A maternal-offspring coadaptation theory for the evolution of genomic imprinting. PLoS Biol 2006 Nov;4(12):e380.

[15] Pijnenborg R, Vercruysse L, Hanssens M. Fetal-maternal conflict, trophoblast invasion, preeclampsia, and the red queen. Hypertens Pregnancy 2008;27(2):183-96.

[16] Odent M. Hypothesis: preeclampsia as a maternal-fetal conflict. MedGenMed 2001 Sep 5;3(5):2.

[17] Romero R, Ghidini A, Mazor M, Behnke E. Microbial invasion of the amniotic cavity in premature rupture of membranes. Clin Obstet Gynecol 1991 Dec;34(4):769-78.

[18] Romero R, Yoon BH, Mazor M, Gomez R, Diamond MP, Kenney JS *et al.* The diagnostic and prognostic value of amniotic fluid white blood cell count, glucose, interleukin-6, and gram stain in patients with preterm labor and intact membranes. Am J Obstet Gynecol 1993 Oct; 169(4):805-16.

[19] DiGiulio DB, Romero R, Amogan HP, Kusanovic JP, Bik EM, Gotsch F *et al.* Microbial prevalence, diversity and abundance in amniotic fluid during preterm labor: a molecular and culture-based investigation. PLoS One 2008; 3(8):e3056.

[20] DiGiulio DB, Romero R, Kusanovic JP, Gomez R, Kim CJ, Seok KS *et al.* Prevalence and diversity of microbes in the amniotic fluid, the fetal inflammatory response, and pregnancy outcome in women with preterm pre-labor rupture of membranes. Am J Reprod Immunol 2010 Jul 1;64(1):38-57.

[21] Ecker DJ, Sampath R, Massire C, Blyn LB, Hall TA, Eshoo MW *et al.* Ibis T5000: a universal biosensor approach for microbiology. Nat Rev Microbiol 2008 Jul;6(7):553-8.

[22] Grant RJ, Baldwin CD, Nalca A, Zoll S, Blyn LB, Eshoo MW *et al.* Application of the Ibis-T5000 pan-Orthopoxvirus assay to quantitatively detect monkeypox viral loads in clinical specimens from macaques experimentally infected with aerosolized monkeypox virus. Am J Trop Med Hyg 2010 Feb;82(2):318-23.

[23] Biasucci G, Rubini M, Riboni S, Morelli L, Bessi E, Retetangos C. Mode of delivery affects the bacterial community in the newborn gut. Early Hum Dev 2010 Jul;86(1):13-5.

[24] Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N *et al.* Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci USA 2010 Jun 29;107(26):11971-5.

[25] Romero R, Espinoza J, Goncalves LF, Kusanovic JP, Friel L, Hassan S. The role of inflammation and infection in preterm birth. Semin Reprod Med 2007 Jan;25(1):21-39.

[26] Romero R, Mazor M, Morrotti R, Avila C, Oyarzun E, Insunza A *et al.* Infection and labor. VII. Microbial invasion of the amniotic cavity in spontaneous rupture of membranes at term. Am J Obstet Gynecol 1992 Jan;166(1 Pt 1):129-33.

[27] Gomez R, Romero R, Nien JK, Chaiworapongsa T, Medina L, Kim YM *et al.* A short cervix in women with preterm labor and intact membranes: a risk factor for microbial invasion of the amniotic cavity. Am J Obstet Gynecol 2005 Mar;192(3):678-89.

[28] Hassan S, Romero R, Hendler I, Gomez R, Khalek N, Espinoza J *et al.* A sonographic short cervix as the only clinical manifestation of intra-amniotic infection. J Perinat Med 2006; 34(1):13-9.

[29] Romero R, Gonzalez R, Sepulveda W, Brandt F, Ramirez M, Sorokin Y *et al.* Infection and labor. VIII. Microbial invasion of the amniotic cavity in patients with suspected cervical incompetence: prevalence and clinical significance. Am J Obstet Gynecol 1992 Oct;167 (4 Pt 1):1086-91.

[30] Madan I, Romero R, Kusanovic JP, Mittal P, Chaiworapongsa T, Dong Z *et al.* The frequency and clinical significance of intra-amniotic infection and/or inflammation in women with placenta previa and vaginal bleeding: an unexpected observation. J Perinat Med 2010 May;38(3):275-9.

[31] Blackwell S, Romero R, Chaiworapongsa T, Kim YM, Bujold E, Espinoza J *et al.* Maternal and fetal inflammatory responses in unexplained fetal death. J Matern Fetal Neonatal Med 2003 Sep;14(3):151-7.

[32] Blackwell S, Romero R, Chaiworapongsa T, Refuerzo J, Gervasi MT, Yoshimatsu J *et al.* Unexplained fetal death is associated with changes in the adaptive limb of the maternal immune response consistent with prior antigenic exposure. J Matern Fetal Neonatal Med 2003 Oct;14(4):241-6.

[33] Goldenberg RL, Thompson C. The infectious origins of stillbirth. Am J Obstet Gynecol 2003 Sep;189(3):861-73.

[34] McClure EM, Goldenberg RL. Infection and stillbirth. Semin Fetal Neonatal Med 2009 Aug;14(4):182-9.

[35] Gomez R, Romero R, Ghezzi F, Yoon BH, Mazor M, Berry SM. The fetal inflammatory response syndrome. Am J Obstet Gynecol 1998 Jul;179(1):194-202.

[36] Gotsch F, Romero R, Kusanovic JP, Mazaki-Tovi S, Pineles BL, Erez O *et al.* The fetal inflammatory response syndrome. Clin Obstet Gynecol 2007 Sep;50(3):652-83.

[37] Madsen-Bouterse SA, Romero R, Tarca AL, Kusanovic JP, Espinoza J, Kim CJ *et al.* The transcriptome of the fetal inflammatory response syndrome. Am J Reprod Immunol 2010 Jan;63(1):73-92.

[38] Romero R, Espinoza J, Goncalves LF, Gomez R, Medina L, Silva M *et al.* Fetal cardiac dysfunction in preterm premature rupture of membranes. J Matern Fetal Neonatal Med 2004 Sep;16(3):146-57.

[39] Romero R, Maymon E, Pacora P, Gomez R, Mazor M, Yoon BH *et al.* Further observations on the fetal inflammatory response syndrome: a potential homeostatic role for the soluble receptors of tumor necrosis factor alpha. Am J Obstet Gynecol 2000 Nov;183(5):1070-7.

[40] Romero R, Savasan ZA, Chaiworapongsa T, Berry SM, Kusanovic JP, Hassan SS *et al.* Hematologic profile of the fetus with systemic inflammatory response syndrome. J Perinat Med 2011 Jan;40(1):19-32.

[41] Yoon BH, Romero R, Yang SH, Jun JK, Kim IO, Choi JH *et al.* Interleukin-6 concentrations in umbilical cord plasma are elevated in neonates with white matter lesions associated with periventricular leukomalacia. Am

J Obstet Gynecol 1996 May;174(5):1433-40.

[42] Chaiworapongsa T, Romero R, Berry SM, Hassan SS, Yoon BH, Edwin S *et al.* The role of granulocyte colony-stimulating factor in the neutrophilia observed in the fetal inflammatory response syndrome. J Perinat Med 2011 Nov;39(6):653-66.

[43] Kim YM, Romero R, Chaiworapongsa T, Espinoza J, Mor G, Kim CJ. Dermatitis as a component of the fetal inflammatory response syndrome is associated with activation of Toll-like receptors in epidermal keratinocytes. Histopathology 2006 Nov;49(5):506-14.

[44] Kannan S, Balakrishnan B, Muzik O, Romero R, Chugani D. Positron emission tomography imaging of neuroinflammation. J Child Neurol 2009 Sep;24(9):1190-9.

[45] Kannan S, Dai H, Navath RS, Balakrishnan B, Jyoti A, Janisse J *et al.* Dendrimer-based postnatal therapy for neuroinflammation and cerebral palsy in a rabbit model. Sci Transl Med 2012 Apr 18;4(130): 130ra46.

[46] Saadani-Makki F, Kannan S, Makki M, Muzik O, Janisse J, Romero R *et al.* Intrauterine endotoxin administration leads to white matter diffusivity changes in newborn rabbits. J Child Neurol 2009 Sep;24(9):1179-89.

[47] Yoon BH, Park CW, Chaiworapongsa T. Intrauterine infection and the development of cerebral palsy. BJOG 2003 Apr;110(20):124-7.

[48] Yoon BH, Romero R, Kim CJ, Koo JN, Choe G, Syn HC *et al.* High expression of tumor necrosis factor-alpha and interleukin-6 in periventricular leukomalacia. Am J Obstet Gynecol 1997 Aug;177(2):406-11.

[49] Yoon BH, Romero R, Park JS, Kim CJ, Kim SH, Choi JH *et al.* Fetal exposure to an intra-amniotic inflammation and the development of cerebral palsy at the age of three years. Am J Obstet Gynecol 2000 Mar;182(3):675-81.

[50] Espinoza J, Chaiworapongsa T, Romero R, Edwin S, Rathnasabapathy C, Gomez R *et al.* Antimicrobial peptides in amniotic fluid: defensins, calprotectin and bacterial/permeability-increasing protein in patients with microbial invasion of the amniotic cavity, intra-amniotic inflammation, preterm labor and premature rupture of membranes. J Matern Fetal Neonatal Med 2003 Jan;13(1):2-21.

[51] Bry K, Lappalainen U, Hallman M. Intraamniotic interleukin-1 accelerates surfactant protein synthesis in fetal rabbits and improves lung stability after premature birth. J Clin Invest 1997 Jun 15;99(12):2992-9.

[52] Dhar V, Hallman M, Lappalainen U, Bry K. Interleukin-1 alpha upregulates the expression of surfactant protein-A in rabbit lung explants. Biol Neonate 1997;71(1):46-52.

[53] Emerson GA, Bry K, Hallman M, Jobe AH, Wada N, Ervin MG *et al.* Intra-amniotic interleukin-1 alpha treatment alters postnatal adaptation in premature lambs. Biol Neonate 1997;72(6):370-9.

[54] Been JV, Zimmermann LJ. Histological chorioamnionitis and respiratory outcome in preterm infants. Arch Dis Child Fetal Neonatal Ed 2009 May;94(3):F218-25.

[55] Romero R, Brody DT, Oyarzun E, Mazor M, Wu YK, Hobbins JC *et al.* Infection and labor. III. Interleukin-1: a signal for the onset of parturition. Am J Obstet Gynecol 1989 May;160(5 Pt 1):1117-23.

[56] Romero R, Manogue KR, Mitchell MD, Wu YK, Oyarzun E, Hobbins JC *et al.* Infection and labor. IV. Cachectin-tumor necrosis factor in the amniotic fluid of women with intraamniotic infection and preterm labor. Am J Obstet Gynecol 1989 Aug;161(2):336-41.

[57] Mitchell MD, Romero RJ, Edwin SS, Trautman MS. Prostaglandins and parturition. Reprod Fertil Dev 1995;7(3):623-32.

[58] Romero R, Emamian M, Wan M, Quintero R, Hobbins JC, Mitchell MD. Prostaglandin concentrations in amniotic fluid of women with intra-amniotic infection and preterm labor. Am J Obstet Gynecol 1987 Dec;157(6): 1461-7.

[59] Romero R, Chaiworapongsa T, Espinoza J, Gomez R, Yoon BH, Edwin S *et al.* Fetal plasma MMP-9 concentrations are elevated in preterm premature rupture of the membranes. Am J Obstet Gynecol 2002 Nov;187(5):1125-30.

[60] Romero R, Gomez R, Ghezzi F, Yoon BH, Mazor M, Edwin SS *et al.* A fetal systemic inflammatory response is followed by the spontaneous onset of preterm parturition. Am J Obstet Gynecol 1998 Jul;179(1):186-93.