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Endocrinology of Parturition

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Reproductive success is critical for survival of the species. The timely onset of labor and delivery is an important determinant of perinatal outcome. Preterm birth (defined as delivery before 37 weeks' gestation) and post-term pregnancy (defined as pregnancy continuing beyond 42 weeks) are both associated with a significant increase in perinatal morbidity and mortality. The factors responsible for the timing of labor in the human are complex and, as yet, are not completely understood. This article reviews the current understanding of the parturition cascade responsible for the spontaneous onset of labor at term and discusses preterm labor and post-term pregnancy.

Historical context

Considerable evidence suggests that the fetus is in control of the timing of labor. Horse–donkey crossbreeding experiments in the 1950s resulted in a gestational length intermediate between that of horses (340 days) and that of donkeys (365 days) [1–3], suggesting a role for the fetal genotype in the initiation of labor. The mechanism by which the fetus triggers labor at term has been demonstrated elegantly in domestic ruminants such as sheep and cows and involves the activation at term of the fetal hypothalamic-pituitary-adrenal (HPA) axis, leading to a surge in adrenal cortisol production. Fetal cortisol then acts to up-regulate directly the activity of placental 17α-hydroxylase/17,20-lyase (CYP17) enzyme, which catalyzes the conversion of pregnenolone to 17β-estradiol. The switch in progesterone:estrogen

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ratio at term provides the impetus for uterine prostaglandin production and labor [4–9]. However, human placentae lack the CYP17 enzyme, which is critical to this pathway [2], and, as such, this mechanism does not apply in humans. During the Hippocratic period, it was believed that the fetus presented head down so that it could kick its legs up against the fundus of the uterus and propel itself through the birth canal. Although we have moved away from this simple and mechanical view of labor, the factors responsible for the initiation and maintenance of labor at term are not well defined. The slow progress in our understanding of labor in humans is the result, in large part, of the absence of an adequate animal model. Parturition in most animals results from changes in circulating hormone levels in the maternal and fetal circulations at the end of pregnancy (endocrine events), whereas labor in humans results from a complex dynamic biochemical dialog that exists between the fetoplacental unit and the mother (paracrine and autocrine events).

Diagnosis of labor

Labor is the physiologic process by which a fetus is expelled from the uterus and is common to all viviparous species. Labor remains a clinical diagnosis. It requires the presence of regular painful uterine contractions, which increase in frequency and intensity, leading to progressive cervical effacement and dilatation. In normal labor, there appears to be a time-dependent relationship between these elements: the biochemical connective tissue changes in the cervix usually precede uterine contractions that, in turn, precede cervical dilatation. All of these events occur usually before spontaneous rupture of the fetal membranes [10]. The mean duration of human singleton pregnancy is 280 days (40 weeks) from the first day of the last normal menstrual period. ''Term'' is defined as the period from 37.0 to 42.0 weeks of gestation.

Parturition cascade at term

It is likely that a parturition cascade exists at term that removes the mechanisms maintaining uterine quiescence and recruits factors promoting uterine activity (Fig. 1) [8,9]. Given its teleologic importance, such a cascade would likely have multiple redundant loops to ensure a fail-safe system of securing pregnancy success and ultimately the preservation of the species. In such a model, each element is connected to the next in a sequential fashion, and many of the elements demonstrate positive feed-forward characteristics typical of a cascade mechanism. The sequential recruitment of signals that serve to augment the labor process suggests that it may not be possible to single out any one signaling mechanism as being responsible for the initiation of labor. It may therefore be prudent to describe such mechanisms as being responsible for promoting, rather than initiating, the process of labor [11].

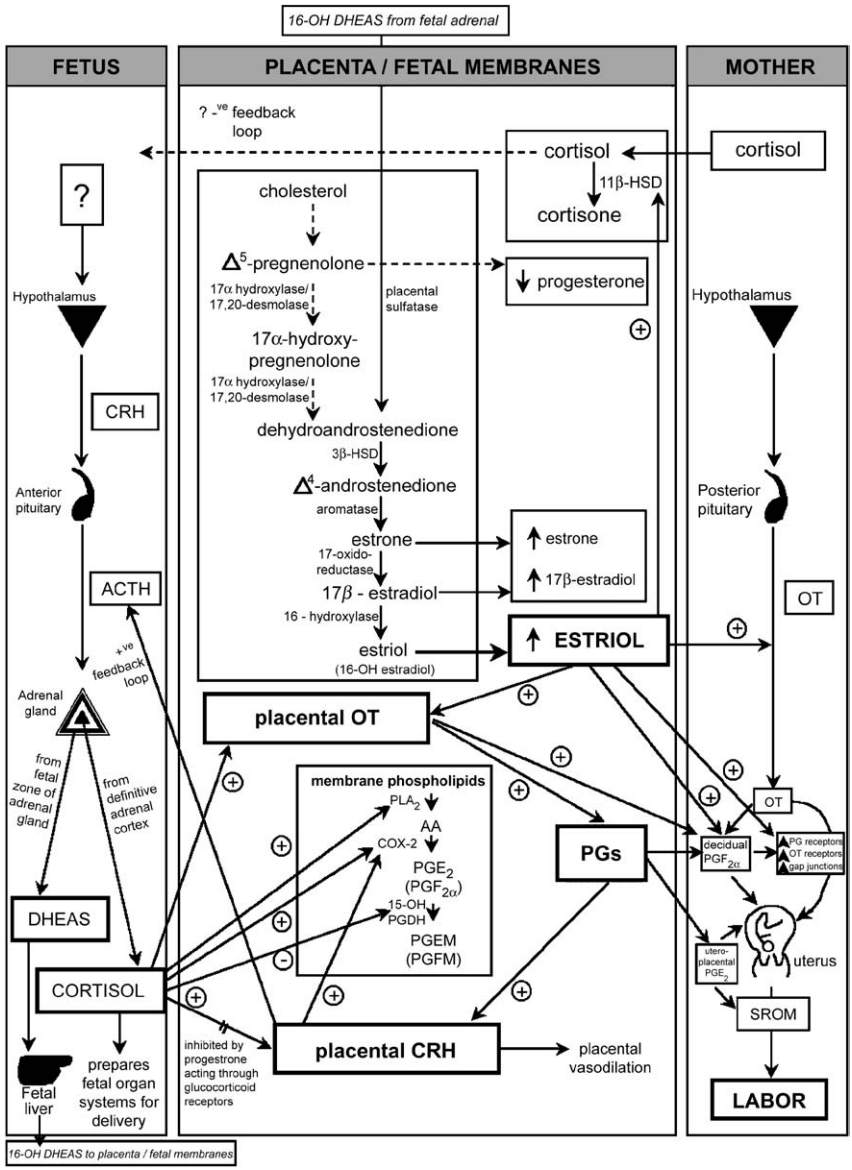

Fig. 1. Proposed parturition cascade for labor induction at term. The spontaneous induction of labor at term in the human is regulated by a series of paracrine-autocrine hormones acting in an integrated parturition cascade responsible for promoting uterine contractions. COX-2, cyclooxygenase 2; OT, oxytocin; PGDH, prostaglandin dehydrogenase; PGEM, 13,14-dihydro-15-keto-PGE_2; PGFM, 13,14-dihydro-15-keto-$PGF_{2\alpha}$; PLA_2, phospholipase A; SROM, spontaneous rupture of the fetal membranes; 11β-HSD, 11β-hydroxysteroid dehydrogenase; 16-OH DHEAS, 16-OH-dehydroepiandrostendione sulfate.

Regardless of whether the trigger for labor begins within or outside the fetus, the final common pathway for labor ends in the maternal tissues of the uterus and is characterized by the development of regular phasic uterine contractions. As in other smooth muscles, myometrial contractions are mediated through the ATP-dependent binding of myosin to actin. In contrast to vascular smooth muscle, however, myometrial cells have a sparse innervation, which is further reduced during pregnancy [12]. The regulation of the contractile mechanism of the uterus is therefore largely humoral or dependent on intrinsic factors within the myometrial cells.

Autocrine and paracrine mediators of parturition

Labor at term may be regarded best physiologically as a release from the inhibitory effects of pregnancy on the myometrium rather than as an active process mediated by uterine stimulants [13]. For example, strips of quiescent term myometrial tissue placed in an isotonic water bath will contract vigorously and spontaneously without added stimuli [13,14]. In vivo, however, it is likely that both mechanisms are important. A comprehensive analysis of each of the individual paracrine-autocrine pathways implicated in the process of labor has been reviewed in detailed elsewhere [8,9,11,15,16]. Briefly, human labor at term is a multifactorial physiologic event involving an integrated set of changes within the maternal tissues of the uterus (myometrium, decidua, and uterine cervix), which occur gradually over a period of days to weeks. Such changes include but are not limited to an increase in prostaglandin synthesis and release within the uterus, an increase in the myometrial gap junction formation, and up-regulation of myometrial oxytocin receptors. Once the myometrium and cervix are prepared, endocrine or paracrine-autocrine factors from the fetoplacental unit bring about a switch in the pattern of myometrial activity from irregular to regular contractions. The fetus may coordinate this switch in myometrial activity through its influence on placental steroid hormone production, through the mechanical distention of the uterus and through the secretion of neurohypophyseal hormones and other stimulators of prostaglandin synthesis. The final common pathway toward labor appears to be the activation of the fetal HPA axis and is probably common to all viviparous species.

Role of the fetal hypothalamic-pituitary-adrenal axis in the onset of labor

Activation of the fetal HPA axis results in enhanced fetal pituitary adrenocorticotropin hormone (ACTH) secretion that leads, in turn, to the release of abundant C19 estrogen precursor dehydroepiandrostenedione sulfate (DHEAS) from the intermediate (fetal) zone of the fetal adrenal. This is because the human placenta is an incomplete steroidogenic organ, and estrogen synthesis by the human placenta has an obligate need for C19 steroid precursor

(see Fig. 1) [16]. DHEAS is converted in the fetal liver to 16-hydroxy DHEAS and then travels to the placenta where it is metabolized into estradiol (E_2), estrone (E_1), and estriol (E_3). In the rhesus monkey, an infusion of C19 precursor (androstenedione) leads to preterm delivery [17]. This effect is blocked by the concurrent infusion of an aromatase inhibitor [18], demonstrating that conversion to estrogen is important. However, a systemic infusion of estrogen failed to induce delivery, suggesting that the action of estrogen is likely paracrine-autocrine [17,19,20]. In addition to DHEAS, the fetal adrenal glands also produce copious amounts of cortisol. Cortisol acts to prepares fetal organ systems for extrauterine life and to promote expression of a number of placental genes, including corticotropin releasing hormone (CRH), oxytocin, and prostaglandins (especially prostaglandin E_2 [PGE_2]).

CRH is a peptide hormone released by the hypothalamus but is also expressed by placental and chorionic trophoblasts and amnionic and decidual cells [21–23]. CRH stimulates pituitary ACTH secretion and adrenal cortisol production. In the mother, cortisol inhibits hypothalamic CRH and pituitary ACTH release, creating a negative feedback loop. In contrast, cortisol stimulates CRH release by the decidual, trophoblastic, and fetal membranes [23–26]. CRH, in turn, further drives maternal and fetal HPA activation, thereby establishing a potent positive feed-forward loop. In normal pregnancy, the increased production of CRH from decidual, trophoblastic, and fetal membranes leads to an increase in circulating cortisol beginning in midgestation [27]. The effects of CRH are enhanced by a fall in maternal plasma CRH-binding protein near term [28]. CRH also enhances prostaglandin production by amnionic, chorionic, and decidual cells [23]. Prostaglandins, in turn, stimulate CRH release from the decidual and fetal membranes [24]. The rise in prostaglandins ultimately results in parturition [29]. CRH also can directly affect myometrial contractility [30]. Taken together, these factors suggest that placental CRH serves as a placental clock that controls the timing of labor [31,32]. A longitudinal measurement of CRH throughout pregnancy suggests that the placental clock may be set to run fast or slow as early as the first or second trimester of pregnancy [31,33–35]. Once the speed of the placental clock is set, the timing of delivery may be predetermined.

Role of estrogens in the onset of labor

Human pregnancy is characterized by a hyperestrogenic state of unparallel magnitude in the entire mammalian kingdom. The placenta is the primary source of estrogens, and concentrations of estrogens increase in the maternal circulation with increasing gestational age. Placental estrone and 17β-estradiol are derived primarily from maternal C19 androgens (testosterone and androstenedione), whereas estriol is derived almost exclusively from the fetal C19 estrogen precursor (DHEAS). Estrogens do not themselves cause uterine contractions but do promote a series of myometrial changes, including increasing the number of prostaglandin receptors, oxytocin

receptors, and gap junctions, and up-regulating the enzymes responsible for muscle contractions (myosin light chain kinase, calmodulin) [36–39] that enhance the capacity of the myometrium to generate contractions.

Role of progesterone in the onset of labor

The administration of a progesterone receptor antagonist such as RU-486 readily induces abortion if given before 7 weeks (49 days) of gestation [40]. Similarly, the surgical removal of the corpus luteum, the source of progesterone, before 7 weeks results in pregnancy loss [41]. Taken together, these data suggest that adequate production of progesterone by the corpus luteum is critical to the maintenance of early pregnancy until the placenta takes over this function at approximately 7 to 9 weeks of gestation (hence, its name: *pro-gest*ational st*er*oid horm*one*). The role of progesterone in later pregnancy, however, is less clear.

In contrast to most animal species, the circulating levels of progesterone during human labor are similar to levels measured 1 week prior [2,42], suggesting that the systemic withdrawal of progesterone is not a prerequisite for labor in humans. This is in contrast to most laboratory animals (with the noted exceptions of the guinea pig and armadillo) in which progesterone withdrawal is an essential component of parturition. However, circulating hormone levels do not necessarily reflect tissue levels, and there is increasing evidence from both in vitro [43–45] and in vivo studies [46–48] that the spontaneous onset of labor at term may be preceded by a physiologic (functional) withdrawal of progesterone activity at the level of the uterus. In one clinical trial, Meis and colleagues [47] randomly assigned 459 patients at high risk for preterm delivery by virtue of a previous preterm birth to receive a weekly intramuscular injection of 17α-hydroxyprogesterone caproate (250 mg) or a matching placebo, beginning at 16 to 20 weeks of gestation and continuing until 36 weeks. Prophylaxis with 17α-hydroxyprogesterone significantly reduced the risk of delivery at less than 37 weeks (36% versus 55% in the placebo group [relative risk [RR], 0.66; 95% CI, 0.54%–0.81%]), less than 35 weeks (21% versus 31% [RR, 0.67; 95% CI, 0.48%–0.93%]), and less than 32 weeks (11% versus 20% [RR, 0.58; 95% CI, 0.37%–0.91%]). Progesterone likely maintains uterine quiescence during the latter half of pregnancy by limiting the production of stimulatory prostaglandins and inhibiting the expression of contraction-associated protein genes (ion channels, oxytocin and prostaglandin receptors, and gap junctions) within the myometrium [9,49]. The molecular mechanisms by which progesterone maintains uterine quiescence are not known, but the progesterone receptor is likely critical to its action. In support of this hypothesis, the administration of the progesterone receptor antagonist RU-486 at term leads to increased uterine activity and the induction of labor [50].

Cortisol and progesterone appear to have antagonistic actions within the fetoplacental unit. For example, cortisol increases prostaglandin production

by the placental and fetal membranes by up-regulating cyclooxygenase-2 (amnion and chorion) and down-regulating 15-hydroxyprostaglandin dehydrogenase (15-OH-PGDH) (chorionic trophoblast), thereby promoting cervical ripening and uterine contractions. Progesterone has the opposite effect [51]. In addition, cortisol has been shown to compete with the inhibitory action of progesterone in the regulation of placental CRH gene expression in primary cultures of human placenta [52]. It is likely, therefore, that the cortisol-dominant environment of the fetoplacental unit just before the onset of labor may act through a series of autocrine-paracrine pathways to overcome the efforts of progesterone to maintain uterine quiescence and prevent myometrial contractions.

Role of other autocrine-paracrine hormones in the onset of labor

Placental oxytocin acts directly on the myometrium to cause contractions and indirectly by up-regulating prostaglandin production, especially prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) by the decidua [53]. $PGF_{2\alpha}$, in turn, is produced primarily by the maternal decidua and acts on the myometrium to up-regulate oxytocin receptors and gap junctions, thereby promoting uterine contractions. PGE_2 is primarily of fetoplacental origin and is likely more important in promoting cervical ripening (maturation) and spontaneous rupture of the fetal membranes.

Preterm labor and birth

Preterm (premature) birth, defined as delivery between 20 and 37 weeks, complicates 7% to 10% of all deliveries [54,55]. Despite intense efforts, the ability of obstetric care providers to prevent preterm labor and birth is limited. Instead of decreasing, the incidence of preterm birth in the United States has continued to rise over the past 2 decades, reaching a peak of 12.1% in 2002 (Fig. 2) [56]. Based on these data, there are approximately 460,000 preterm births in the United States each year. Prematurity is the leading cause of perinatal death in nonanomalous newborns in the United States. Even at gestational ages in which survival is relatively assured, significant morbidity is still common. For example, Robertson and colleagues [57] reported that, at 30 weeks' gestation, the risk of respiratory distress syndrome in surviving infants is 50%, and necrotizing enterocolitis will develop in 11% and intraventricular hemorrhage in 5%.

Causes of preterm birth

Preterm labor likely represents a syndrome rather than a single diagnosis because the causes are varied. Approximately 20% of all preterm deliveries are iatrogenic and are performed for maternal or fetal indications, including intrauterine growth restriction, preeclampsia, placenta previa, and nonreassuring fetal testing [8]. Of the remaining cases of preterm birth,

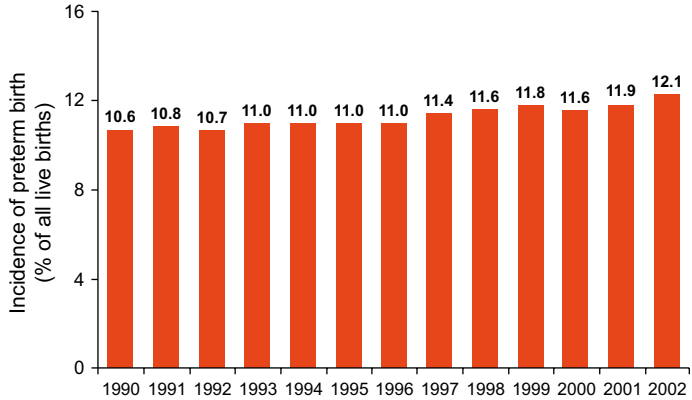

Fig. 2. Preterm births in the United States, 1990–2002. (*Data from* the National Center for Health Statistics, final natality data, and the March of Dimes Perinatal Data Center, 2003. Available at http://marchofdimes.com/peristats.)

approximately 30% occur in the setting of preterm premature rupture of the membranes (pPROM), 20% to 25% result from intra-amniotic infection, and the remaining 25% to 30% are caused by spontaneous (unexplained) preterm labor (Fig. 3) [8,58].

Preterm labor may reflect a breakdown of the normal mechanisms responsible for maintaining uterine quiescence throughout gestation. For example, the choriodecidua is enriched selectively with 15-OH-PGDH, the enzyme responsible for degrading the primary (biologically active) prostaglandins. A deficiency in choriodecidual 15-OH-PGDH activity may impair the ability of the fetal membranes to metabolize the primary prostaglandins, thereby allowing PGE_2 to reach the myometrium and initiate contractions. Such a deficiency has been described and may account for up to 15% of idiopathic preterm labor [59]. Alternatively, premature labor may represent a

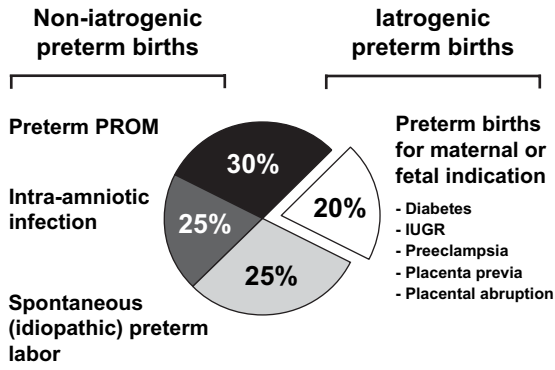

Fig. 3. Causes of preterm births. (*Data from* Tucker JM, Goldenberg RL, Davis RO, et al. Etiologies of preterm birth in an indigent population: is prevention a logical expectation? Obstet Gynecol 1991;77:343–7.)

short-circuiting or overwhelming of the normal parturition cascade. Indeed, a feature of the proposed parturition cascade would be the ability of the fetoplacental unit to trigger labor prematurely if the intrauterine environment became hostile and threatened the well being of the fetus. For example, up to 30% of preterm labors are believed to result from intra-amniotic infection [58]. In many patients with infection, elevated levels of lipoxygenase and cyclooxygenase pathway products can be demonstrated [58,60]. There are also increased concentrations of cytokines (including interleukin [IL]-1β, IL-6, and tumor necrosis factor [TNF]-α) in the amniotic fluid of such women [61]. Cytokines and eicosanoids appear to accelerate each other's production in a cascade-like fashion, which may act to overwhelm the normal parturition cascade, resulting in preterm labor. Recently, thrombin has been shown to be a powerful uterotonic agent [62,63], providing a physiologic mechanism for preterm labor secondary to placental abruption.

Molecular mechanisms of preterm labor

Clinical and experimental evidence links most preterm births to four distinct pathogenic processes. Although these four pathogenic processes can and often do occur simultaneously, each has a unique biochemical and biophysical signature with variable temporal manifestations and distinct epidemiologic profiles. Regardless of the initiating event, these processes converge on a final common biologic pathway characterized by cervical and fetal membrane extracellular matrix degradation and myometrial activation, leading to uterine contractions that increase in frequency and intensity cervical change (preterm labor) with or without pPROM.

Premature activation of the maternal or fetal hypothalamic-pituitary-adrenal axis

Premature activation of the fetal or maternal HPA axes is evident in up to 33% of preterm births [64]. Maternal physical and psychologic stress leads to the premature activation of the maternal HPA axis and has been linked consistently to preterm birth [65–67]. The activation of the fetal HPA axis has been associated with preterm delivery, and uteroplacental insufficiency is a source of fetal stress [64,68,69]. Indeed, chronic hypertension and severe pregnancy-induced hypertension are associated with an increase of 36% and 300%, respectively, in spontaneous preterm birth [70]. Both maternal and fetal stress likely cause preterm labor by increasing the release of placental CRH, which, in turn, programs the placental clock (Fig. 4) [71,72]. Recent studies have noted elevated second trimester maternal serum CRH concentrations among patients who deliver preterm [33,73,74].

Decidual and amniochorionic inflammation

Laboratory and clinical data show a consistent association between spontaneous preterm labor and genital tract infections [75,76]. The final common

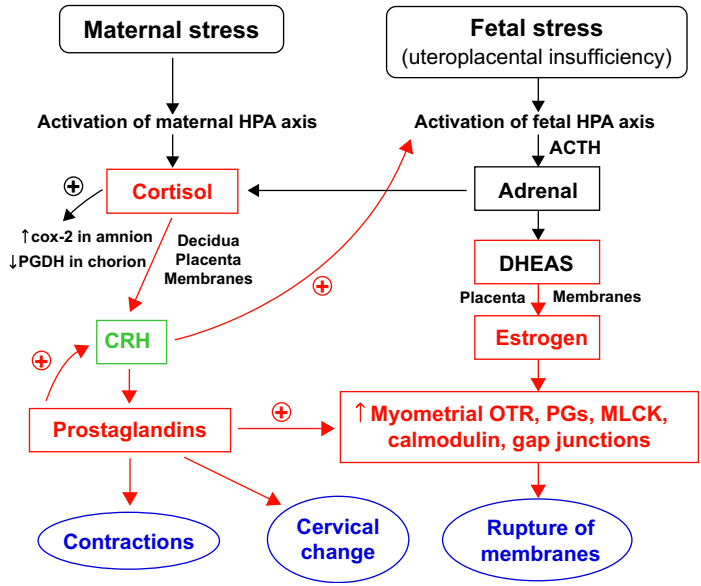

Fig. 4. Maternal and fetal HPA axis and preterm birth. COX-2, cyclooxygenase 2; MLCK, myosin light chain kinase; OTR, oxytocin receptors; PGDH, prostaglandin dehydrogenase.

pathway is a maternal or fetal inflammatory response that is likely triggered by infection in the decidua or amniochorion, with release of inflammatory mediators (cytokines, matrix metalloproteinases [MMPs]) by activated macrophages and granulocytes. In one histopathologic study [77], for example, evidence of chorioamnionitis was observed in 70% of patients with preterm birth associated with pPROM. IL-1, IL-6, and TNF-α directly stimulate PGE_2 and $PGF_{2\alpha}$ production and inhibit their metabolism in the chorion [78,79]. Cytokines also induce MMPs (collagenase, gelatinase, and stromelysins) that weaken the fetal membranes and ripen the cervix by disrupting the normally rigid collagen extracellular matrix (Fig. 5). TNF-α may play an additional role because it can induce apoptosis. Elevated circulating levels of TNF-α have been associated with pPROM [80].

Midtrimester cervicovaginal IL-6 [81] and plasma granulocyte colony-stimulating factor levels [82] also are elevated in asymptomatic women who subsequently deliver preterm, but the sensitivity and positive predictive values of these tests are only approximately 50%. The fetus can also initiate a systemic inflammatory cytokine response leading to labor. One study of 41 women who had pPROM showed that microbial invasion of the uterine cavity elicited an increase in fetal IL-6 levels that was associated with impending preterm labor and birth [83]. Taken together, these data support the hypothesis that many instances of spontaneous preterm labor results from an inflammatory process associated with the activation of the genital tract

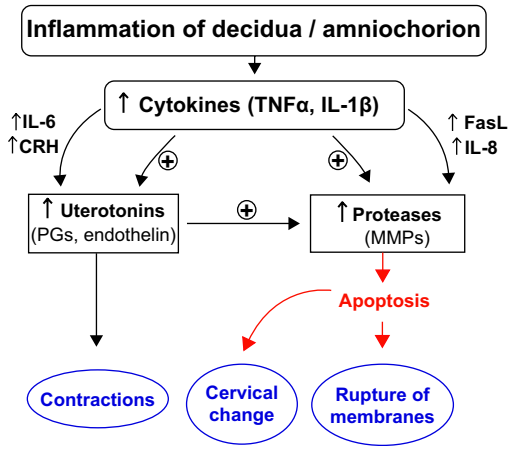

Fig. 5. Inflammation of decidua-amniochorion and preterm labor. FasL, fas ligand.

cytokine network and the presence of cytokines in the maternal or fetal compartment several weeks before delivery.

Decidual hemorrhage

Decidual hemorrhage (abruption) presenting as vaginal bleeding in more than one trimester of pregnancy is associated with a three- and sevenfold increased risk, respectively, of preterm birth [84] and pPROM [85]. The risk of preterm birth is even higher (100-fold) in such women if they also had a previous pregnancy complicated by pPROM [86]. The causes of decidual hemorrhage-associated preterm birth include older, parous, married, and college-educated women [87], a profile quite distinct from that of both infection- and stress-mediated preterm labor.

Thrombin, a plasma protease that converts fibrinogen into fibrin, is formed from prothrombin by the action of prothrombinase (factor Xa). Recent studies have shown that thrombin stimulates myometrial contractions by activating phosphatidylinositol-signaling pathways in a dose-dependent fashion [88]. Thrombin also increases expression of plasminogen activators and MMPs (Fig. 6) [89,90]. The release of thrombin associated with placental abruption may therefore directly initiate the final common pathway leading to preterm labor.

Pathologic uterine distention

Excessive uterine stretching caused by multiple-birth pregnancy or polyhydramnios is associated with preterm labor. Preterm birth rates exceed 50% for twin pregnancies, 80% for triplet pregnancies, and 90% for quadruplet pregnancies. The mechanism is not clear but appears to involve a signal initiated by the mechanical stretching of uterine myometrial, cervical, and fetal membrane cells that is transmitted through the cellular

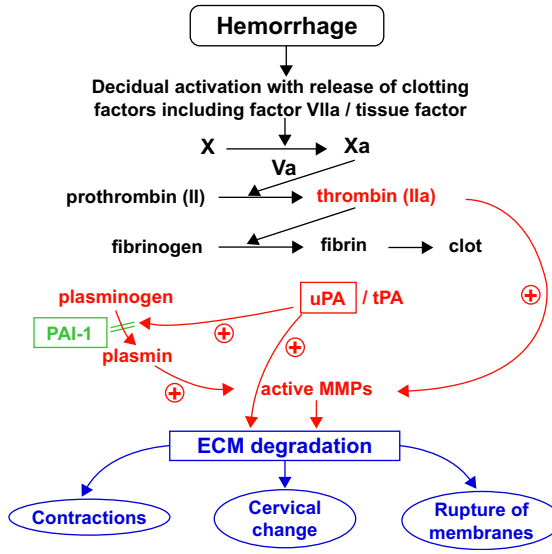

Fig. 6. Hemorrhage and preterm labor. ECM, extracellular matrix; PAI-1, plasminogen activator inhibitor 1; tPA, tissue-type plasminogen activator; uPA, urokinase plasminogen activator.

cytoskeleton and leads to the activation of cellular protein kinases (Fig. 7) [91]. Three genes have recently been identified whose expression in the membranes is up-regulated by acute distention in vitro and in association with labor: an interferon-stimulated gene encoding a 54-kD protein, the gene for Huntington-interacting protein 2 (an ubiquitin-conjugating enzyme), and a novel as yet unidentified transcript [92]. The precise role of these factors in parturition is not known.

Post-term pregnancy

Post-term (prolonged) pregnancy is defined as a pregnancy that has extended to or beyond 42 weeks (294 days) from the first day of the last normal menstrual period or 14 days beyond the best obstetric estimate of the date of delivery [93]. Because of the heterogeneity of populations, definitions, the use of ultrasonography, and local practice patterns (such as the routine induction of labor at term and the management of parturients who previously have undergone cesarean delivery), the reported incidence of pregnancies continuing beyond the estimated date of delivery varies widely. In the United States, approximately 18% of all births occur after 41 weeks, 3% to 14% (mean 10%) occur after 42 weeks and are therefore post-term, and 4% of pregnancies will continue to or beyond 43 weeks in the absence of obstetric intervention [94,95]. The routine early use of ultrasonography to accurately date pregnancies can reduce the rate of false-positive diagnoses and thereby

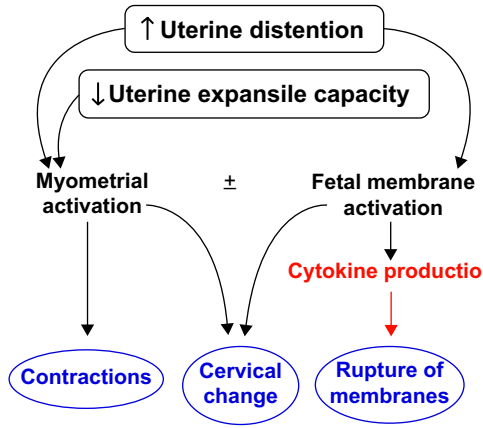

Fig. 7. Uterine distension and preterm labor.

the overall rate of post-term pregnancy from 10% to approximately 1% to 3% [96–99].

Causes of post-term pregnancy

As discussed previously, the most common cause of prolonged pregnancy is an error in gestational age dating. In most cases, the cause of true post-term pregnancy is not known. Risk factors include nulliparity and a previous post-term pregnancy [100,101]. Recent data have also shown an association with male fetuses [102]. Rarer causes include placental sulfatase deficiency, fetal adrenal insufficiency, or fetal anencephaly (in the absence of polyhydramnios). The increased risk of post-term pregnancy in women who have had previous post-term pregnancy suggests an underlying biologic or genetic cause, which has yet to be defined adequately [101,103].

Complications of post-term pregnancy

Recent studies have shown that the risks to the fetus [104–108] and mother [107,109,110] of continuing the pregnancy beyond the estimated date of delivery is greater than appreciated originally. Antepartum stillbirths account for more perinatal deaths than either complications of prematurity or sudden infant death syndrome [106]. Once a fetus is delivered, it is no longer at risk of intrauterine fetal demise (stillbirth). When pregnancies exceed 42 weeks, perinatal mortality (stillbirths plus early neonatal deaths) increases to 4 to 7 per 1000 deliveries compared with 2 to 3 per 1000 deliveries at 40 weeks [111,112]. Perinatal mortality at 43 weeks' gestation is fourfold higher than that at 40 weeks and is five- to sevenfold higher at 44 weeks [112]. Post-term pregnancy is also an independent risk factor for neonatal encephalopathy [113] and for death in the first year of life [105–107]. Since

the risks of the routine induction of labor (primarily failed induction leading to cesarean delivery) are lower than reported previously [114,115], recent consensus opinions recommend the routine induction of labor at an earlier gestation age, specifically 41 weeks' gestation [93,107].

Summary

Labor is a complex physiologic process involving fetal, placental, and maternal signals. The timely onset of labor and birth is an important determinant of perinatal outcome. Both preterm labor and delivery and post-term pregnancy are associated with increased perinatal morbidity and mortality. Considerable evidence suggests that the fetus is in control of the timing of labor and, thus, its birth, but exactly how this is achieved in the human is still unknown. A better understanding of the mechanisms responsible for the process of labor will further our knowledge about disorders of parturition, such as preterm labor, and improve the ability of obstetric care providers to secure a successful pregnancy outcome.

References

[1] Liggins GC. The onset of labour: an overview. In: McNellis D, Challis JRG, MacDonald PC, et al, editors. The onset of labor: cellular and integrative mechanisms: a National Institute of Child Health and Human Development research planning workshop (November 29–December 1, 1987). Ithaca (NY): Perinatology Press; 1988. p. 1–3.
[2] Liggins GC. Initiation of labor. Biol Neonate 1989;55:366–94.
[3] Turnbull AC, Anderson AB. Evidence of a foetal role in determining the length of gestation. Postgrad Med J 1969;45:65–7.
[4] Liggins BJ, Fairclough RJ, Grieves SA, et al. The mechanism of initiation of parturition in the ewe. Recent Prog Horm Res 1973;29:111–59.
[5] Flint APF, Anderson ABM, Steele PA, et al. The mechanism by which fetal cortisol controls the onset of parturition in the sheep. Biochem Soc Trans 1975;3:1189–94.
[6] Thorburn GD, Hollingworth SA, Hooper SB. The trigger for parturition in sheep: fetal hypothalamus or placenta? J Dev Physiol 1991;15:71–9.
[7] Matthews SG, Challis JRG. Regulation of the hypothalamo-pituitary-adreno-cortical axis in fetal sheep. Trends Endocrinol Metab 1996;4:239–46.
[8] Norwitz ER, Robinson JN, Challis JR. The control of labor. N Engl J Med 1999;341:660–6.
[9] Challis JRG, Matthews SG, Gibb W, et al. Endocrine and paracrine regulation of birth at term and preterm. Endocr Rev 2000;21:514–50.
[10] Duff P, Huff RW, Gibbs RS. Management of premature rupture of membranes and unfavorable cervix in term pregnancy. Obstet Gynecol 1984;63:697–702.
[11] Myers DA, Nathanielsz PW. Biologic basis of term and preterm labor. Clin Perinatol 1993; 20:9–28.
[12] Pauerstein CJ, Zauder HL. Autonomic innervation, sex steroids and uterine contractility. Obstet Gynecol Surv 1970;25:617–30.
[13] López Bernal A, Rivera J, Europe-Finner GN, et al. Parturition: activation of stimulatory pathways or loss of uterine quiescence? Adv Exp Med Biol 1995;395:435–51.
[14] Garrioch DB. The effect of indomethacin on spontaneous activity in the isolated human myometrium and on the response to oxytocin and prostaglandin. Br J Obstet Gynaecol 1978;85:47–52.

[15] Honnebier MB, Nathanielsz PW. Primate parturition and the role of the maternal circadian system. Eur J Obstet Gynecol Reprod Biol 1994;55:193–203.
[16] Nathanielsz PW. Comparative studies on the initiation of labor. Eur J Obstet Gynecol Reprod Biol 1998;78:127–32.
[17] Mecenas CA, Giussani DA, Owiny JR, et al. Production of premature delivery in pregnant rhesus monkeys by androstenedione infusion. Nat Med 1996;2:442–8.
[18] Giussani DA, Jenkins SL, Mecenas CA, et al. Daily and hourly temporal association between delta4-androstenedione-induced preterm myometrial contractions and maternal plasma estradiol and oxytocin concentrations in the 0.8 gestation rhesus monkey. Am J Obstet Gynecol 1996;174:1050–5.
[19] Figueroa JP, Honnebier MBOM, Binienda Z, et al. Effect of 48 hour intravenous Δ^4-androstenedione infusion on pregnant rhesus monkeys in the last third of gestation: Changes in maternal plasma estradiol concentrations and myometrial contractility. Am J Obstet Gynecol 1989;161:481–6.
[20] Nathanielsz PW, Jenkins SL, Tame JD, et al. Local paracrine effects of estradiol are central to parturition in the rhesus monkey. Nat Med 1998;4:456–9.
[21] Zoumakis E, Makrigiannakis A, Margioris AN, et al. Endometrial corticotropin-releasing hormone: its potential autocrine and paracrine actions. Ann N Y Acad Sci 1997;828:84–94.
[22] Petraglia F, Potter E, Cameron VA, et al. Corticotropin-releasing factor-binding protein is produced by human placenta and intrauterine tissues. J Clin Endocrinol Metab 1993;77: 919–24.
[23] Jones SA, Brooks AN, Challis JR. Steroids modulate corticotropin-releasing hormone production in human fetal membranes and placenta. J Clin Endocrinol Metab 1989;68:825–30.
[24] Petraglai F, Coukos G, Volpe A, et al. Involvement of placental neurohormones in human parturition. Ann N Y Acad Sci 1991;622:331–40.
[25] Smith R, Mesiano S, Chan EC, Brown S, et al. Corticotropin-releasing hormone directly and preferentially stimulates dehydroepiandrosterone sulfate secretion by human fetal adrenal cortical cells. J Clin Endocrinol Metab 1998;83:2916–20.
[26] Chakravorty A, Mesiano S, Jaffe RB. Corticotropin-releasing hormone stimulates P450 17alpha- hydroxylase/17,20-lyase in human fetal adrenal cells via protein kinase C. J Clin Endocrinol Metab 1999;84:3732–8.
[27] Lockwood CJ, Radunovic N, Nastic D, et al. Corticotropin-releasing hormone and related pituitary-adrenal axis hormones in fetal and maternal blood during the second half of pregnancy. J Perinat Med 1996;24:243–51.
[28] Perkins AV, Eben F, Wolfe CD, et al. Plasma measurements of corticotrophin-releasing hormone-binding protein in normal and abnormal human pregnancy. J Endocrinol 1993; 138:149–57.
[29] Gibb W. The role of prostaglandins in human parturition. Ann Med 1998;30:235–41.
[30] Grammatopoulos DK, Hillhouse EW. Role of corticotropin-releasing hormone in onset of labor. Lancet 1999;354:1546–9.
[31] McLean M, Bisits A, Davies J, et al. A placental clock controlling the length of human pregnancy. Nat Med 1995;1:460–3.
[32] Korebrits C, Ramirez MM, Watson L, et al. Maternal corticotropin-releasing hormone is increased with impending preterm birth. J Clin Endocrinol Metab 1998;83:1585–91.
[33] Hobel CJ, Dunkel-Schetter C, Roesch SC, et al. Maternal plasma corticotropin-releasing hormone associated with stress at 20 weeks' gestation in pregnancies ending in preterm delivery. Am J Obstet Gynecol 1999;180(1 Pt 3):S257–63.
[34] Wadhwa PD, Porto M, Garite TJ, et al. Maternal corticotropin-releasing hormone levels in the early third trimester predicts length of gestation in human pregnancy. Am J Obstet Gynecol 1998;179:1079–85.
[35] Leung TN, Chung TK, Madsen G, et al. Elevated mid-trimester maternal corticotrophin-releasing hormone levels in pregnancies that delivered before 34 weeks. Br J Obstet Gynaecol 1999;106:1041–6.

[36] Lye SJ, Nicholson BJ, Mascarenhas M, et al. Increased expression of connexin-43 in the rat myometrium during labor is associated with an increase in the plasma estrogen:progesterone ratio. Endocrinology 1993;132:2380–6.
[37] Bale TL, Dorsa DM. Cloning, novel promoter sequence, and estrogen regulation of a rat oxytocin receptor gene. Endocrinology 1997;138:1151–8.
[38] Windmoller R, Lye SJ, Challis JR. Estradiol modulation of ovine uterine activity. Can J Physiol Pharmacol 1983;61:722–8.
[39] Matsui K, Higashi K, Fukunaga K, et al. Hormone treatments and pregnancy alter myosin light chain kinase and calmodulin levels in rabbit myometrium. J Endocrinol 1983;97:11–9.
[40] Peyron R, Aubeny E, Targosz V, et al. Early termination of pregnancy with mifepristone (RU 486) and the orally active prostaglandin misoprostol. N Engl J Med 1993;328:1509–13.
[41] Csapo AI, Pulkkinen M. Indispensability of the human corpus luteum in the maintenance of early pregnancy: luteectomy evidence. Obstet Gynecol Surv 1978;33:69–81.
[42] Hanssens MC, Selby C, Symonds EM. Sex steroid hormone concentrations in preterm labour and the outcome of treatment with ritodrine. Br J Obstet Gynaecol 1985;92:698–702.
[43] Madsen G, Zakar T, Ku CY, et al. Prostaglandins differentially modulate progesterone receptor-A and -B expression in human myometrial cells: evidence for prostaglandin-induced functional progesterone withdrawal. J Clin Endocrinol Metab 2004;89:1010–3.
[44] Grazzini E, Guillon G, Mouillac B, et al. Inhibition of oxytocin receptor function by direct binding of progesterone. Nature 1998;392:509–12.
[45] Condon JC, Jeyasuria P, Faust JM, et al. A decline in the levels of progesterone receptor coactivators in the pregnant uterus at term may antagonize progesterone receptor function and contribute to the initiation of parturition. Proc Natl Acad Sci U S A 2003;100:9518–23.
[46] Keirse MJNC. Progestogen administration in pregnancy may prevent preterm delivery. Br J Obstet Gynaecol 1990;97:149–54.
[47] Meis PJ, Klebanoff M, Thom E, et al. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003;348:2379–85.
[48] Da Fonseca EB, Bittar RE, Carvalho MH, et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol 2003;188:419–24.
[49] Norwitz ER, Schust DJ, Fisher SJ. Implantation and the survival of early pregnancy. N Engl J Med 2001;345:1400–8.
[50] Neilson JP. Mifepristone for induction of labour. Cochrane Database Syst Rev 2000:(4); CD002865.
[51] Challis JR, Sloboda DM, Alfaidy N, et al. Prostaglandins and mechanisms of preterm birth. Reproduction 2002;124:1–17.
[52] Karalis K, Goodwin G, Majzoub JA. Cortisol blockade of progesterone: a possible molecular mechanism involved in the initiation of human labor. Nat Med 1996;2:556–60.
[53] Wilson T, Liggins GC, Whittaker DJ. Oxytocin stimulates the release of arachidonic acid and prostaglandin F2 alpha from human decidual cells. Prostaglandins 1988;35:771–80.
[54] Rush RW, Keirse MJNC, Howat P, et al. Contribution of preterm delivery to perinatal mortality. BMJ 1976;2:965–8.
[55] Villar J, Ezcurra EJ, de la Fuente VG, et al. Preterm delivery syndrome: the unmet need. Res Clin Forums 1994;16:9–33.
[56] Martin JA, Hamilton BE, Sutton PD, et al. Births: final data for 2002. Natl Vital Stat Rep 2003;52:1.
[57] Robertson PA, Sniderman SH, Laros RK Jr, et al. Neonatal morbidity according to gestational age and birth weight from five tertiary care centers in the United States, 1983 through 1986. Am J Obstet Gynecol 1992;166:1629–41.
[58] Romero R, Avila C, Brekus CA, et al. The role of systemic and intrauterine infection in preterm parturition. Ann N Y Acad Sci 1991;662:355–75.

[59] Matthews SG, Challis JRG. Regulation of the hypothalamo-pituitary-adreno-cortical axis in fetal sheep. Trends Endocrinol Metab 1996;4:239.
[60] Dudley DJ. Preterm labor: an intra-uterine inflammatory response syndrome? J Reprod Immunol 1997;36:93–109.
[61] Romero R, Emamian M, Wan M, et al. Prostaglandin concentrations in amniotic fluid of women with intra-amniotic infection and preterm labor. Am J Obstet Gynecol 1987;157: 1461–7.
[62] Elovitz MA, Saunders T, Ascher-Landsberg J, et al. Effects of thrombin on myometrial contractions in vitro and in vivo. Am J Obstet Gynecol 2000;183:799–804.
[63] Elovitz M, Baron J, Phillippe M. The role of thrombin in preterm parturition. Am J Obstet Gynecol 2001;185:1059–63.
[64] Arias F, Rodriquez L, Rayne SC, et al. Maternal placental vasculopathy and infection: two distinct subgroups among patients with preterm labor and preterm ruptured membranes. Am J Obstet Gynecol 1993;168:585–91.
[65] Berkowitz GS, Kasl SV. The role of psychosocial factors in spontaneous preterm delivery. J Psychosom Res 1983;27:283–90.
[66] Lobel M, Dunkel-Schetter C, Scrimshaw SC. Prenatal maternal stress and prematurity: a prospective study of socioeconomically disadvantaged women. Health Psychol 1992;11: 32–40.
[67] Copper RL, Goldenberg RL, Das A, et al, for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. The preterm prediction study: maternal stress is associated with spontaneous preterm birth at less than thirty-five weeks' gestation. Am J Obstet Gynecol 1996;175:1286–92.
[68] Ott WJ. Intrauterine growth retardation and preterm delivery. Am J Obstet Gynecol 1993; 168:1710–5.
[69] Salafia CM, Ghidini A, Lopez-Zeno JA, et al. Uteroplacental pathology and maternal arterial mean blood pressure in spontaneous prematurity. J Soc Gynecol Investig 1998;5: 68–71.
[70] Kramer MS, McLean FH, Eason EL, et al. Maternal nutrition and spontaneous preterm birth. Am J Epidemiol 1992;136:574–83.
[71] McLean M, Bisits A, Davies J, et al. A placental clock controlling the length of human pregnancy. Nat Med 1995;1:460–3.
[72] Korebrits C, Ramirez MM, Watson L, et al. Maternal corticotropin-releasing hormone is increased with impending preterm birth. J Clin Endocrinol Metab 1998;83:1585–91.
[73] Wadhwa PD, Porto M, Garite TJ, et al. Maternal corticotropin-releasing hormone levels in the early third trimester predict length of gestation in human pregnancy. Am J Obstet Gynecol 1998;179:1079–85.
[74] Leung TN, Chung TK, Madsen G, et al. Elevated mid-trimester maternal corticotrophin-releasing hormone levels in pregnancies that delivered before 34 weeks. Br J Obstet Gynaecol 1999;106:1041–6.
[75] Lockwood CJ, Kuczynski E. Markers of risk for preterm delivery. J Perinat Med 1999;27: 5–20.
[76] Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med 2000;342:1500–7.
[77] Moretti M, Sibai BM. Maternal and perinatal outcome of expectant management of premature rupture of membranes in the midtrimester. Am J Obstet Gynecol 1988;159:390–6.
[78] Romero R, Durum S, Dinarello CA, et al. Interleukin-1 stimulates prostaglandin biosynthesis by human amnion. Prostaglandins 1989;37:13–22.
[79] Van Mier CA, Sangha RK, Walton JC, et al. Immunoreactive 15-hydroxyprostaglandin dehydrogenase (PGDH) is reduced in fetal membranes from patients at preterm delivery in the presence of infection. Placenta 1996;17:291–7.
[80] Lei H, Furth EE, Kalluri R, et al. A program of cell death and extracellular matrix degradation is activated in the amnion before the onset of labor. J Clin Invest 1996;98:1971–8.

[81] Lockwood CJ, Ghidini A, Wein R, et al. Increased interleukin-6 concentrations in cervical secretions are associated with preterm delivery. Am J Obstet Gynecol 1994;171:1097–102.
[82] Goldenberg RL, Andrews WW, Mercer BM, et al, for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. The preterm prediction study: granulocyte colony-stimulating factor and spontaneous preterm birth. Am J Obstet Gynecol 2000;182:625–30.
[83] Yoon BH, Romero R, Jun JK, et al. Amniotic fluid cytokines (interleukin-6, tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-8) and the risk for the development of bronchopulmonary dysplasia. Am J Obstet Gynecol 1997;177:825–30.
[84] Williams MA, Mittendorf R, Lieberman E, et al. Adverse infant outcomes associated with first-trimester vaginal bleeding. Obstet Gynecol 1991;78:14–8.
[85] Harger JH, Hsing AW, Tuomala RE, et al. Risk factors for preterm premature rupture of fetal membranes: a multicenter case-control study. Am J Obstet Gynecol 1990;163: 130–7.
[86] Ekwo EE, Gosselink CA, Moawad A. Unfavorable outcome in penultimate pregnancy and premature rupture of membranes in successive pregnancy. Obstet Gynecol 1992;80:166–72.
[87] Strobino B, Pantel-Silverman J. Gestational vaginal bleeding and pregnancy outcome. Am J Epidemiol 1989;129:806–15.
[88] Elovitz MA, Ascher-Landsberg J, Saunders T, et al. The mechanisms underlying the stimulatory effects of thrombin on myometrial smooth muscle. Am J Obstet Gynecol 2000;183: 674–81.
[89] Rosen T, Schatz F, Kuczynshi E, et al. Thrombin-enhanced matrix metalloproteinase-1 expression: a mechanism linking placental abruption with premature rupture of the membranes. J Matern Fetal Neonatal Med 2002;11:11–7.
[90] Lockwood CJ, Krikun G, Aigner S, et al. Effects of thrombin on steroid-modulated cultured endometrial stromal cell fibrinolytic potential. J Clin Endocrinol Metab 1996;81: 107–12.
[91] Ou CW, Orsino A, Lye SJ. Expression of connexin-43 and connexin-26 in the rat myometrium during pregnancy and labor is differentially regulated by mechanical and hormonal signals. Endocrinology 1997;138:5398–407.
[92] Nemeth E, Millar LK, Bryant-Greenwood G. Fetal membrane distention: II. differentially expressed genes regulated by acute distention in vitro. Am J Obstet Gynecol 2000;182:60–7.
[93] American College of Obstetricians and Gynecologists. Management of postterm pregnancy. ACOG Practice Bulletin No. 55. 2004.
[94] Ventura SJ, Martin JA, Curtin SC, et al. Births: final data for 1998. Natl Vital Stat Rep 2000;48:1–100.
[95] Bakketeig LS, Bergsjo P. Post-term pregnancy: magnitude of the problem. In: Chalmers I, Enkin M, Keirse M, editors. Effective care in pregnancy and childbirth. Oxford: Oxford University Press; 1991.
[96] Boyd ME, Usher RH, McLean FH, et al. Obstetric consequences of postmaturity. Am J Obstet Gynecol 1988;158:334–8.
[97] Gardosi J, Vanner T, Francis A. Gestational age and induction of labor for prolonged pregnancy. Br J Obstet Gynaecol 1997;104:792–7.
[98] Taipale P, Hiilermaa V. Predicting delivery date by ultrasound and last menstrual period on early gestation. Obstet Gynecol 2001;97:189–94.
[99] Neilson JP. Ultrasound for fetal assessment in early pregnancy. Cochrane Database Syst Rev 2000; CD000182.
[100] Alfirevic Z, Walkinshaw SA. Management of post-term pregnancy: to induce or not? Br J Hosp Med 1994;52:218–21.
[101] Mogren I, Stenlund H, Hogberg U. Recurrence of prolonged pregnancy. Int J Epidemiol 1999;28:253–7.
[102] Divon MY, Ferber A, Nisell H, et al. Male gender predisposes to prolongation of pregnancy. Am J Obstet Gynecol 2002;187:1081–3.

[103] Olesen AW, Basso O, Olsen J. Risk of recurrence of prolonged pregnancy. BMJ 2003;326: 476.
[104] Herabutya Y, Prasertsawat PO, Tongyai T, et al. Prolonged pregnancy: the management dilemma. Int J Gynecol Obstet 1992;37:253–8.
[105] Hilder L, Costeloe K, Thilaganathan B. Prolonged pregnancy: evaluating gestation-specific risks of fetal and infant mortality. Br J Obstet Gynaecol 1998;105:169–73.
[106] Cotzias CS, Paterson-Brown S, Fisk NM. Prospective risk of unexplained stillbirth in singleton pregnancies at term: population based analysis. BMJ 1999;319:287–8.
[107] Rand L, Robinson JN, Economy KE, et al. Post-term induction of labor revisited. Obstet Gynecol 2000;96:779–83.
[108] Smith GC. Life-table analysis of the risk of perinatal death at term and post term in singleton pregnancies. Am J Obstet Gynecol 2001;184:489–96.
[109] Alexander JM, McIntire DD, Leveno KJ. Forty weeks and beyond: pregnancy outcomes by week of gestation. Obstet Gynecol 2000;96:291–4.
[110] Treger M, Hallak M, Silberstein T, et al. Post-term pregnancy: should induction of labor be considered before 42 weeks? J Matern Fetal Neonatal Med 2002;11:50–3.
[111] Bakketeig LS, Bergsjo P. Post-term pregnancy: magnitude of the problem. In: Enkin M, Keirse MJ, Chalmers I, editors. Effective care in pregnancy and childbirth. Oxford: Oxford University Press; 1989.
[112] Feldman GB. Prospective risk of stillbirth. Obstet Gynecol 1992;79:547–53.
[113] Badawi N, Kurinczuk JJ, Keogh JM, et al. Antepartum risk factors for newborn encephalopathy: the Western Australian case-control study. BMJ 1998;317:1549–53.
[114] Hannah ME, Hannah WJ, Hellmann J, et alfor the Canadian Multicenter Post-Term Pregnancy Trial Group. Induction of labor as compared with serial antenatal monitoring in post-term pregnancy: a randomized controlled trial. N Engl J Med 1992;326:1587–92.
[115] Hannah ME, Hannah WJ, Willan A. Comment on the effectiveness of induction of labor for postterm pregnancy. Am J Obstet Gynecol 1994;170:716–23.