REVIEW ARTICLE

MECHANISMS OF DISEASE

Parturition

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THE MECHANISMS THAT INSTIGATE PARTURITION IN HUMANS HAVE BEEN remarkably elusive, but some parts of the puzzle have begun to come together. A key change in the field was the realization that human parturition is a distinctly human event — animal models can reveal only limited insights. Consequently, investigators of human parturition have come to understand that they must focus on the pregnant woman, despite the ethical difficulties in conducting studies that involve women in labor.

Preterm birth occurs in 5 to 15% of pregnancies, depending on the population.[1] The rates are rising in many developed countries, and there is a particularly high incidence of preterm birth among black Americans. Assisted reproduction, which can increase the frequency of multiple gestations, is only a partial explanation.[2] Birth before 37 weeks of gestation is associated with 70% of neonatal deaths, and there is a strong inverse association between the perinatal death rate and the period of gestation.

Infant morbidity is also related to a short period of gestation. In a Swedish study, 50% of children with cerebral palsy had been born prematurely.[3] Although there has been no reduction in the incidence of preterm birth over the past 30 years, the development of neonatal intensive care has improved survival considerably. The short-term costs of neonatal intensive care are extremely high, and the long-term costs of medical and educational services for a child who was born prematurely make preterm birth particularly expensive.[4]

THE UNIQUENESS OF HUMAN PARTURITION

Within the class Mammalia, individual species show considerable similarity in many aspects of physiology. Reproduction, however, is an important exception. The development of a placenta is a common feature of reproduction in most mammals, but variations on the theme of parturition among placental mammals are considerable. For example, parturition in sheep is initiated by processes involving the fetal hypothalamus, pituitary, and adrenal glands,[5,6] whereas parturition in goats depends on dissolution of the maternal corpus luteum.[7] Haig has argued that the heterogeneity in mechanisms of parturition is due to a maternal–paternal genetic conflict[8]: paternal genes promote the provisioning of the fetus from maternal resources, whereas maternal genes modify fetal nutrition to preserve resources for the provisioning of later offspring, which may arise from a different father.

Comparative genomic analyses have revealed that almost 95% of human and chimpanzee DNA sequences are shared,[9,10] but one of the greatest differences between the two species occur in genes related to reproduction. In addition, striking changes in the female pelvis with the assumption of an upright posture by the human ancestor australopithecus and increases in the size of the cranium as modern humans evolved have had consequences for parturition (Fig 1).[11]

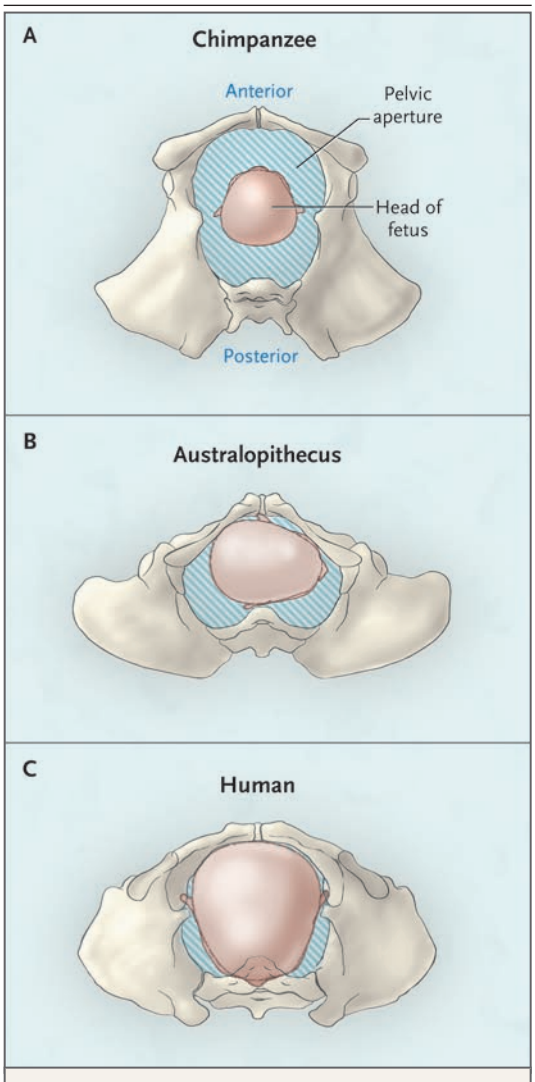


Figure 1. The Chimpanzee, Australopithecus, and Human Pelvises.

The large aperture of the chimpanzee pelvis (Panel A) permits easy passage of the relatively small head of the fetus in an occiput posterior position. In australopithecus (Panel B), the widening of the ilium associated with upright posture and the anteroposterior narrowing of the pelvic aperture require delivery of the head in a lateral position. The human pelvis (Panel C) has an aperture just large enough to allow passage of the head of the fetus in an occiput anterior position.

CORTICOTROPIN-RELEASING HORMONE AND THE TIMING OF BIRTH

Human pregnancy lasts for approximately 38 weeks after conception, with minor variations among ethnic groups.[12] The timing of birth in mice is closely linked to the maturation of the fetal lungs.[13] In humans, by contrast, the timing of birth is associated with the development of the placenta — in particular, with expression of the gene for corticotropin-releasing hormone (CRH) by the placenta.[14]

MATERNAL CRH

Several studies have shown an association between levels of maternal plasma CRH, which is of placental origin, and the timing of birth.[15-19] Maternal plasma CRH levels increase exponentially as pregnancy advances, peaking at the time of delivery. In women who deliver preterm, the exponential increase is rapid, whereas in women who deliver after the estimated date of delivery, the rise is slower.[14,20] These findings suggest that a placental clock determines the timing of delivery.[14]

Production of CRH by the placenta is restricted to primates.[21-25] In monkeys, there is a midgestation peak in placental CRH production, but only in great apes is there an exponential rise similar to that in humans. Humans and great apes also produce a circulating binding protein for CRH (CRHBP). At the end of pregnancy, CRHBP levels fall, thereby increasing the bioavailability of CRH.[26,27] Glucocorticoids stimulate expression of the *CRH* gene and production of CRH by the placenta.[11,28-30] In turn, CRH stimulates the pituitary to produce corticotropin, which causes the adrenal cortex to release cortisol. This arrangement permits a positive feed-forward system that has been shown by mathematical modeling to mimic the changes actually observed in human pregnancy.[31] Placental CRH production is also modified by estrogen, progesterone, and nitric oxide, which are inhibitory, and by a range of neuropeptides, which are stimulatory.[32-35] In an individual woman, the rising levels of placental CRH in maternal blood follow an exponential function that is characteristic for that particular pregnancy. Small changes in the exponential function describing CRH production lead to large differences among different women later in pregnancy. Not all cases of preterm birth are related to changes in placental CRH production; in particular, intrauterine infection, a relatively frequent cause of preterm birth, is not associated with elevated placental CRH production. For this reason, a low level of maternal plasma CRH does not rule out preterm birth. A single CRH measurement has relatively low sensitivity for predicting preterm birth, although in an individual woman, a high

CRH level has a relatively specific association with a greatly increased risk of preterm birth. Given the large variations among pregnant women, it is likely that the rate of increase in maternal CRH levels is the most accurate predictor of the outcome of pregnancy and is the critical variable.[36,37] In assessing CRH values, it is necessary to adjust for race or ethnic group. Black American women have lower maternal plasma CRH levels than other racial or ethnic groups, although among black American women, CRH concentrations do correlate with the timing of birth.[38,39]

CRH RECEPTORS

CRH is secreted from the placenta predominantly into the maternal blood, but it also enters the fetal circulation.[40] CRH acts primarily by binding to the CRH type 1 receptor, a member of the seven-transmembrane G protein–coupled receptor superfamily.[38] In the mother, CRH receptors are present in the pituitary, the myometrium, and probably the adrenal glands. In the fetus, there are CRH receptors in the pituitary, the adrenal glands, and perhaps the lungs. Rising levels of CRH can therefore act at multiple sites in mother and fetus to initiate the changes associated with parturition.

Increased placental CRH levels drive the rise in maternal cortisol and corticotropin levels as gestation advances, although the effect is moderated by the circulating binding protein and the desensitization of CRH receptors by continuous exposure to high levels of CRH.[39,41] The increased levels of CRH and corticotropin promote the production of cortisol and dehydroepiandrosterone sulfate (DHEAS) by the maternal adrenal glands; the increased cortisol may stimulate further placental release of CRH, and DHEAS provides a substrate for placental estrogen synthesis.

There are several forms of CRH receptors in the myometrium.[42] Ligand binding to the most common form, CRHR1α, causes the dissociation of the α subunit of the G protein, which relays signals from the CRH receptor to intracellular effectors. These signals culminate in relaxation of the myometrial cell. At term, CRH receptors change to a form that is less efficient in activating relaxation pathways in the myometrium. Instead, the receptors activate the Gαq pathway, which is linked to protein kinase C activation, and the contractile pathways.[43] CRH has been reported to potentiate the contractile effects of several uterotonins, such as oxytocin and prostaglandin $F_{2\alpha}$, that promote uterine contraction,[44,45] but it has been difficult to replicate these findings.

CRH IN THE FETUS

Placental CRH is also released into the fetus, and although the concentrations are lower in the fetal circulation than in the maternal circulation, they still rise with advancing gestation[46] (Fig. 2). In the fetus, CRH receptors are present in the pituitary[47] and on the cells that form the fetal zone of the adrenal gland.[48] Stimulation of the fetal pituitary by CRH increases corticotropin production and, consequently, the synthesis of cortisol by the fetal adrenal gland and maturation of the fetal lungs. In turn, the rising cortisol concentrations in the fetus further stimulate placental CRH production. The maturation of the fetal lungs as a result of increasing cortisol concentrations is associated with increased production of surfactant protein A and phospholipids, both of which have proinflammatory actions and may stimulate myometrial contractility through increased production of prostaglandins by fetal membranes and the myometrium itself. In baboons, CRH directly stimulates fetal lung development and strongly induces surfactant phospholipid synthesis,[49] but it is not clear whether this occurs in humans.

CRH stimulation of fetal adrenal zone cells, which lack 3β-hydroxysteroid dehydrogenase, preferentially causes placental formation of DHEA, the precursor of estrogen and an important hormone in pregnancy.[48] The fetal zone of the adrenal glands involutes rapidly after delivery of the placenta, indicating that placental factors, such as CRH, maintain the fetal zone (Fig. 2). Thus, CRH may stimulate adrenal steroidogenesis, thereby providing the substrate for the placental production of estrogens, which favor parturition by inducing contraction.[43]

In summary, it appears that positive feedforward systems in the mother and fetus drive an exponential increase in placental CRH production as gestation advances. Increased placental CRH production, in turn, instigates a change in fetal cortisol concentrations, fetal lung maturation, amniotic fluid proteins, phospholipids, and myometrial receptor expression, which combine, through a set of independent activating pathways, to precipitate labor and delivery. These pathways, each capable of stimulating parturition, make the mechanism of labor robust.

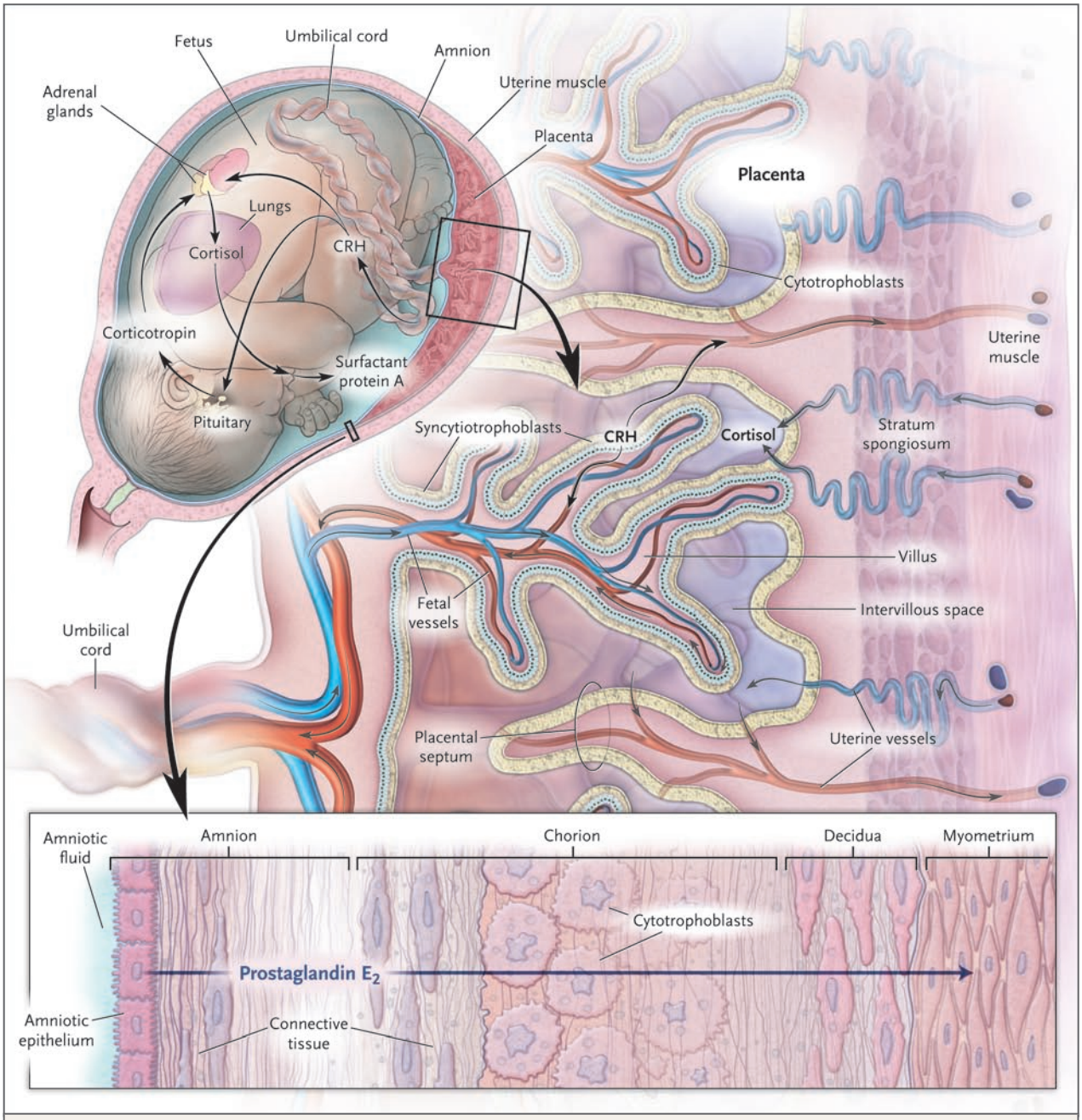


Figure 2. Maternal–Fetal Interactions.

In the intervillous space, the syncytiotrophoblasts release CRH, progesterone, and estrogens into the maternal blood and into the fetal blood. Cortisol passes through a maternal artery and enters the intervillous space, where it stimulates the production of CRH by the syncytiotrophoblasts. A fetal umbilical vein carries CRH into the fetal circulation, stimulating the fetal pituitary to synthesize corticotropin and drive fetal adrenal cortisol and DHEAS synthesis. Cortisol and CRH stimulate the fetal lungs to produce surfactant protein A, which moves from the amniotic fluid to the amnion, where it stimulates the production of cyclooxygenase 2 (COX-2) and the synthesis of prostaglandin E_2. They pass along the chorion and decidua and stimulate the underlying maternal myometrial cells to synthesize additional COX-2 and prostaglandin $F_{2\alpha}$.

ACTIVATION OF THE MYOMETRIUM AT TERM

An important event in labor is the expression of a group of proteins termed "contraction-associated proteins."[50] These proteins act within the uterus, which is in a relaxed state for most of pregnancy, to initiate the powerful rhythmic contractions that force the fetus through a softening cervix at term. There are three types of contraction-associated proteins: those that enhance the interactions between the actin and myosin proteins that cause muscle contraction, those that increase the excitability of individual myometrial cells, and those that promote the intercellular connectivity that permits the development of synchronous contractions (Fig. 3).

PROTEINS THAT PROMOTE MYOCYTE CONTRACTILITY

Interactions between actin and myosin determine myocyte contractility. For these interactions to occur, actin must be converted from a globular to a filamentous form. Actin must also attach to the cytoskeleton at focal points in the cell membrane that allow the development of tension; these focal points link the cell to the underlying matrix.[51,52] Actin's partner, myosin, is activated when it is phosphorylated by myosin light-chain kinase. Calmodulin and increased intracellular calcium activate this enzyme.[53] Phosphorylation of myosin light chains can also be increased by blocking the action of phosphatases.[54] After the myocyte depolarizes, an influx of extracellular calcium through voltage-regulated calcium channels and the release of calcium from intracellular stores[55] result in increased intracellular calcium, thereby promoting myosin–actin interactions and, consequently, contraction.

Nifedipine, an agent that inhibits labor, works by blocking voltage-regulated calcium channels. The channels open when an activating ligand (e.g., prostaglandin) reduces the electrochemical gradient across the myocyte membrane (Fig. 4). These ligand-regulated channels, which release calcium from intracellular stores, are activated by prostaglandins through the E and F prostaglandin receptors[56,57] and by oxytocin, which activates the $G\alpha_q$ proteins linked to phospholipase C.[58,59] Activated phospholipase C, in turn, activates protein kinase C and releases inositol triphosphate. Protein kinase C probably activates myosin light-chain kinase, and inositol triphosphate releases calcium from intracellular stores.[53] The stretching of the myometrium as a result of fetal growth may contribute to the contractility of the myocyte through the action of mitogen-activated protein kinase.[60] Systems that promote relaxation through $G\alpha_2$ pathways oppose these pathways by increasing intracellular cyclic AMP and activating protein kinase A. These enzymes inactivate myosin light-chain kinase. At the time of labor, a shift in the balance of these opposing systems promotes myocyte contraction.[61,62]

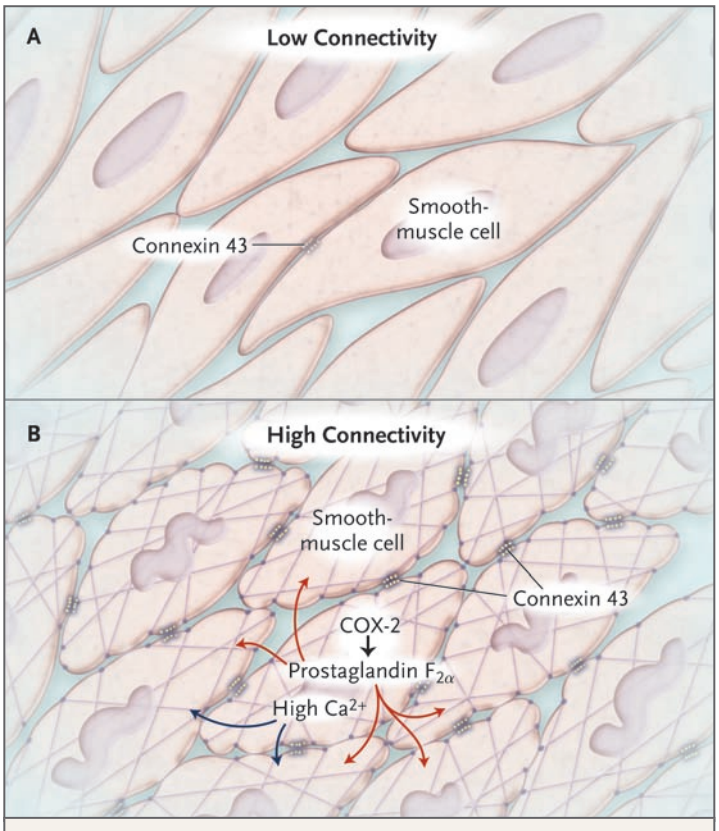


Figure 3. The Uterine Myometrium during Labor.

During labor, the uterine myometrium is converted from a tissue with relatively low connectivity between individual myocytes (Panel A) into a tissue with extensive physical connections (Panel B). The physical connections occur through pores formed by multimers of connexin 43. Connections between myocytes during labor are also formed by paracrine release of prostaglandin $F_{2\alpha}$ and local release of calcium. This extensive physical and biochemical connectivity allows the depolarization in individual myocytes to be passed to neighboring cells and thus form extensive waves of depolarization and contraction over large areas of the uterus. This causes increased intrauterine pressure and progressive distention of the cervix, leading to expulsion of the fetus.

PROTEINS THAT INCREASE MYOCYTE EXCITABILITY

Myocytes maintain an electrochemical potential gradient across the plasma membrane, with the interior negative to the exterior, through the action of the sodium–potassium exchange pump.[55] A component of this process is a potassium channel, which is calcium- and voltage-regulated and allows efflux of potassium, thereby increasing the potential difference across the cell membrane and making it less likely to depolarize (Fig. 4). At the time of labor, changes in the distribution and function of these channels[63,64] lower the intensity of the stimulus required to depolarize myocytes and to produce the associated influx of calcium that generates contraction.[65] β_2- and β_3-sympathomimetic receptors that increase the opening of potassium channels, thereby reducing the excitability of the cell, also decline at labor.[66,67]

PROTEINS THAT PROMOTE INTERCELLULAR CONNECTIVITY

A critical aspect of myometrial activity at labor is the development of synchrony.[68] Synchronous activity of myometrial cells results in the powerful contractions needed to expel the fetus. Equally important are the intervening periods of relaxation, which permit blood flow to the fetus (during contraction, blood flow to the fetus decreases, and during relaxation, it increases). The uterus lacks a pacemaker that regulates the contractions, although specialized pacemaker-like cells have recently been identified.[69] However, as parturition progresses, there is increasing synchronization of the electrical activity of the uterus.[70-72] At the cellular level, this synchrony is achieved by electrical conduction through connecting myofibrils, which transmit the electrical activity to nearby muscle fibers. The activated myocytes produce prostaglandins, which act in a paracrine fashion to depolarize neighboring myocytes. This process leads to a wave of activity as more and more myocytes are recruited into the contraction. After contraction, the myocytes relax and become refractory to further stimulation. The typical uterine contraction consists of a slow rise and fall of tension lasting close to a minute.[73] At the molecular level, myocytes are connected by channels or gap junctions that are created by multimers of connexin 43; these channels allow the myocytes to function in concert (Fig. 3).

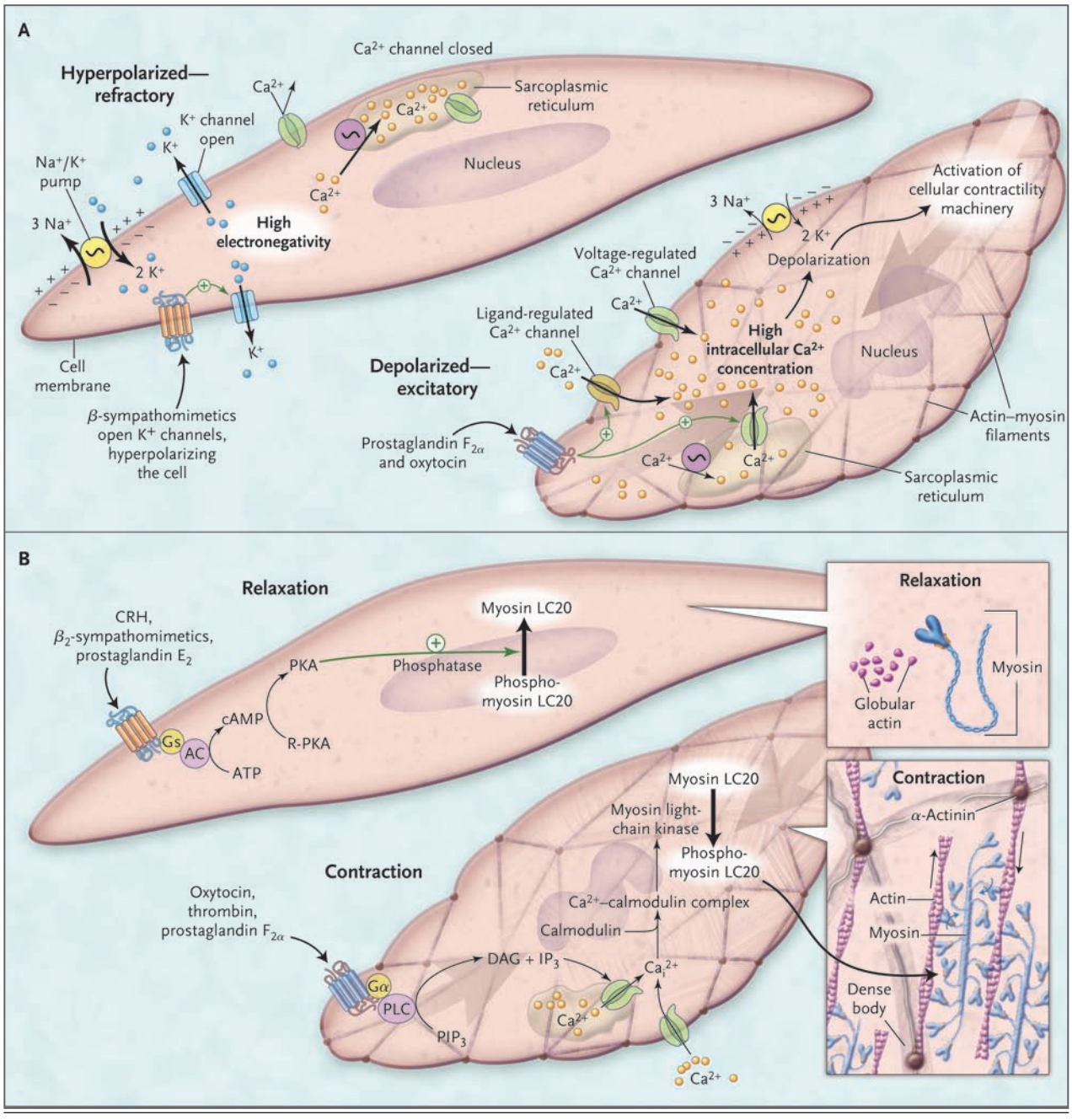
Figure 4 (facing page). Relaxation and Contraction of Uterine Myocytes.

As shown in Panel A, before labor begins, the myocyte maintains a relatively high interior electronegativity, which reduces the likelihood of depolarization and contraction. The resting membrane potential is created by the ATPase-driven sodium–potassium pump, which extrudes three sodium ions for every two potassium ions that are transported into the cell. Open potassium channels allow potassium to leave the cell, following the concentration gradient and further increasing the intracellular electronegativity. Myometrial cell-surface receptors for β-sympathomimetics help to maintain relaxation by promoting the opening of potassium channels. At the time of labor, depolarization occurs when prostaglandin $F_{2\alpha}$ and oxytocin bind to cell-surface receptors, thereby promoting the opening of ligand-regulated calcium channels. Activation of these receptors also promotes release of calcium ions from sarcoplasmic reticulum stores. As the calcium begins to enter the cell, the drop in electronegativity promotes the opening of large numbers of voltage-regulated calcium channels, producing a rapid movement of calcium ions into the cell and, consequently, depolarization. As shown in Panel B, before labor the myocytes of the uterus are maintained in a relaxed state by a range of factors that increase intracellular cyclic AMP (cAMP). The increase in cAMP activates protein kinase A, which promotes phosphodiesterase activity and dephosphorylation of myosin light-chain kinase. The phosphorylation of the myosin light chain is critical for contraction in the uterine myocyte. Relaxation is also promoted by processes that tend to maintain actin in a globular form and prevent formation of the actin fibrils required for contraction. At the time of labor, these processes are reversed. Within the myocytes, actin assumes a fibrillar form. Calcium enters the depolarizing cell and combines with calmodulin to form calmodulin–calcium complexes that activate myosin light-chain kinase, which in turn phosphorylates the myosin light chain. The phosphorylation of the myosin light chain causes the generation of ATPase activity, which promotes the sliding of myosin over the actin filaments and the movement that constitutes contraction. PKA denotes active catalytic protein kinase A, R-PKA inactive PKA, IP_3 inositol triphosphate, PIP_3 phosphatidylinositol-3,4,5-triphosphate, PLC phospholipase C, and DAG diacylglycerol.

THE PATHWAY TO MYOMETRIAL ACTIVATION

FETAL CONTRIBUTIONS TO PARTURITION

During pregnancy, the growth of the uterus under the action of estrogens gives the fetus space for its own growth, but uterine growth ceases



toward the end of pregnancy, and the consequent increasing tension of the uterine wall signals the onset of parturition. On average, labor starts earlier with twins than with singletons and earlier with triplets than with twins, and fetuses with macrosomia or polyhydramnios are often premature; these trends are probably related to the increased myometrial stretching that occurs with multiple or abnormally large fetuses or excess amniotic fluid.[74] In most smooth-muscle organs, stretching leads to contraction.[75] The switch from the growth-accommodating behavior of the uterus during most of pregnancy to the stretch induced by the cessation of uterine growth at labor appears

to be regulated by progesterone.[76] It is likely that progesterone withdrawal increases the attachment of myocytes to the intercellular matrix, through integrins, and this process promotes activation of mitogen-associated protein kinase and increases contractility.[77]

As term approaches, there are increasing concentrations of placental CRH, a boost in the synthesis of corticotropin by the fetal pituitary, and heightened steroidogenesis in the fetal adrenal glands. The DHEA produced in increasing amounts in the fetal zone is rapidly metabolized by the placenta into estrogens. Concurrently, cortisol production is increased in the definitive zone of the fetal adrenal glands.[78] Rising fetal concentrations of cortisol induce maturation of many fetal tissues, especially the lungs.[79] The maturing fetal lungs increase production of the surfactant proteins and phospholipids that are critical for lung function. The surfactant proteins also enter the amniotic fluid, where they have macrophage-activating properties. In the mouse, surfactant protein A activates amniotic fluid macrophages, and these cells play a critical role in the onset of labor.[13] In humans, the amniotic fluid surfactant proteins may well stimulate the inflammation that is observed in the adjacent fetal membranes, cervix, and underlying myometrium at the time of labor. There is considerable evidence that this inflammatory process is one of the elements leading to the onset of labor.[80] During the last weeks of pregnancy, CRH levels also rise in the amniotic fluid, which is in direct contact with the underlying amnion.[81,82]

FETAL MEMBRANE ACTIVATION

The amnion lies in direct contact with the amniotic fluid, giving constituents of the amniotic fluid unrestricted access to the amnion (Fig. 2). The production of surfactant proteins, phospholipids, and inflammatory cytokines in the amniotic fluid increases as cyclooxygenase-2 (COX-2) activity and prostaglandin E_2 production increase in the amnion. Concurrently, levels of cortisol and CRH, both of which stimulate the production of COX-2, rise in the amniotic fluid.[81,83,84] These redundant actions increase prostaglandin E_2 and other mediators of inflammation in the amnion.[85]

The chorion underlies the amnion (Fig. 2). It produces the enzyme prostaglandin dehydrogenase (PGDH), which is a potent inactivator of prostaglandins. Late in pregnancy, chorionic PGDH activity falls, exposing the underlying decidua, cervix, and myometrium to the proinflammatory actions of prostaglandin E_2.[86] Prostaglandins mediate the release of the metalloproteases that weaken the placental membranes, thereby facilitating membrane rupture. CRH also stimulates the secretion of membrane matrix metalloprotease-9.[87]

CERVICAL SOFTENING

A critical component of normal parturition is the softening of the cervix. Parturition is associated with movement of an inflammatory infiltrate into the cervix and the release of metalloproteases that degrade collagen, thus changing the structure of the cervix.[88-90] During this process, the junction between fetal membranes and the decidua breaks down, and an adhesive protein, fetal fibronectin, enters vaginal fluids. The presence of fetal fibronectin in cervical fluids is a clinically useful predictor of imminent delivery.[91,92]

PROGESTERONE WITHDRAWAL

Progesterone plays a critical role in the development of the endometrium by allowing implantation and, subsequently, the maintenance of myometrial relaxation.[93,94] In many mammals, a drop in circulating progesterone levels precipitates parturition; in humans, the progesterone antagonist RU486 can initiate parturition at any time during pregnancy.[95] A characteristic of human pregnancy is that the level of circulating progesterone does not fall with the onset of labor.[96] A search for mechanisms that could account for a functional withdrawal of progesterone has identified several forms of the progesterone receptor. These variants arise from transcription of the single progesterone receptor gene at alternative start sites.[97,98] Progesterone receptor B, the most common transcript, mediates many of the actions of progesterone; there are shorter transcripts, however, including progesterone receptors A and C. These variant receptors lack an N-terminal–activating domain, and in some settings they function as dominant repressors of the function of the progesterone receptor B.[97,99] With the onset of labor, the proportions of progesterone receptors A, B, and C change in a way that could constitute a mechanism of progesterone withdrawal.[100,101] In addition, the function of progesterone receptors requires specific coactivators, including the progesterone receptor coactivators cAMP-response element-binding protein and ste-

roid receptor coactivators 2 and 3,[102] which decrease in abundance with the onset of labor.[102] Progesterone can be metabolized to products with different biologic properties. For example, at the time of labor, the potent relaxation-inducing steroid 5β-dihydroprogesterone decreases as steroid 5β-reductase expression and activity drop.[103] Nuclear transcription factor $\kappa\beta$ may also be important in blocking the action of progesterone at the receptor level.[85]

INFLAMMATION AND THE ONSET OF LABOR

In rhesus monkeys and baboons, parturition at term lasts for several days. Synchronized uterine contractions occur each night, disappearing during the day, until delivery.[104,105] Humans also have the potential to go into and out of active contractions, which implies a degree of reversibility of the process, at least in the early stages. Tissue from human myometrium removed at cesarean section before the onset of labor and placed in an organ bath under tension exhibits regular synchronized contraction[74]; evidently, the contractile machinery is present and capable of activity before the physiologic activation of labor. A study comparing myometrial tissue samples obtained at cesarean section from women in labor with samples obtained before the onset of labor has shown that in both sets of samples, genes that encode participants in inflammation, notably interleukin-8 and superoxide dismutase, are consistently up-regulated.[96]

Understanding the progression to labor in humans has proven difficult because of the lack of

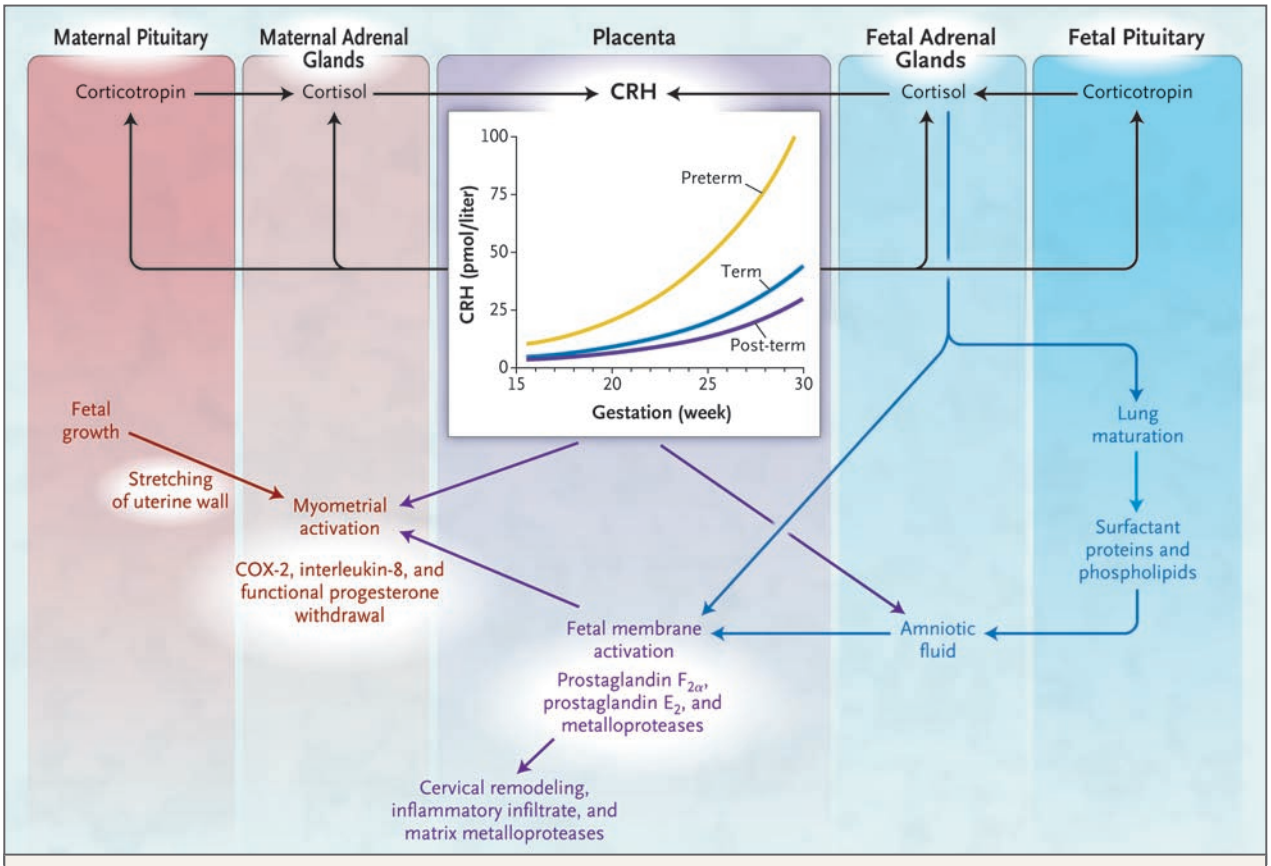


Figure 5. Maternal and Fetal Endocrine Systems Involved in Increased Placental Production of CRH.

Increased placental synthesis of CRH drives increased corticotropin and cortisol production in both mother and fetus. Increased cortisol stimulates further production of CRH, generating a positive feed-forward loop and a consequent exponential rise in CRH synthesis. The increased fetal cortisol leads to lung maturation, increased lung surfactant, and phospholipid production. Cortisol and surfactant proteins activate inflammatory pathways in the amnion, leading to both cervical softening and myometrial activation. The myometrial activation involves progesterone withdrawal and increased production of COX-2, which synthesizes prostaglandins and promotes contraction. Fetal growth and consequent uterine myometrial stretching combine with progesterone withdrawal to further promote uterine contractility.

a good experimental model, but improved modeling techniques may advance our knowledge of the processes involved (Fig. 5). Directed graphs (showing the direction of influence between variables) that model competing hypotheses can be used to determine the compatibility of a particular causal pathway with data from a group of samples in a statistically rigorous manner.[106] With this approach, it appears that increases in inflammatory factors such as COX-2 and interleukin-8 are early events in the progression to active labor. These increases antedate changes in progesterone receptors, which instigate alterations in estrogen receptors and, as a consequence, expression of connexin 43 and the oxytocin receptor (Fig. 5).

A better understanding of the pathway to normal birth should provide the basis for identifying points along the pathway at which a pathological process may precipitate preterm birth. The effects of stress may be mediated by increased cortisol levels in the maternal or fetal compartments and consequent increases in placental *CRH* expression.[107-109] Infection activates inflammation and may stimulate prostaglandin synthesis in fetal membranes. Abruption appears to affect the myometrium directly through the release of thrombin, a potent stimulator of myometrial contraction.[110] In the case of multiple gestation and polyhydramnios, increased uterine stretching activates myometrial contractility (Fig. 4).

The road to an understanding of human birth is circuitous and challenging. The goal is to predict which pregnancies carry a risk of preterm birth and to intervene with appropriate measures. The benefit will be substantial if we are able to reduce the incidences of cerebral palsy and cognitive impairment associated with preterm birth.

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