Tisztelt Enökség, kedves Kolléganők és Kollégák, Hölgyeim és Uraim !

Az eléggé ismeretlen, megoldatlan, bonyolult téma megérdemelne egy interdiszciplináris szakértői konferenciát; a jelen, zanzásított bemutatásom a figyelem felkeltését célozza.

A SZÜLÉS BEINDULÁSA: MECHANIZMUS ÉS JELENTŐSÉG

Kérdések:

- **mi indítja be a szülést?**
- **hogy miért pont 40 hét múlva?**
  - A szülés megindulásának titkai
- **egyáltalán: mi az, ami megismerhető?**
- **miért ilyen korán?**
  - Van-e a témának különlegessége a koraszülés vonatkozásában?

*

Válaszok

*

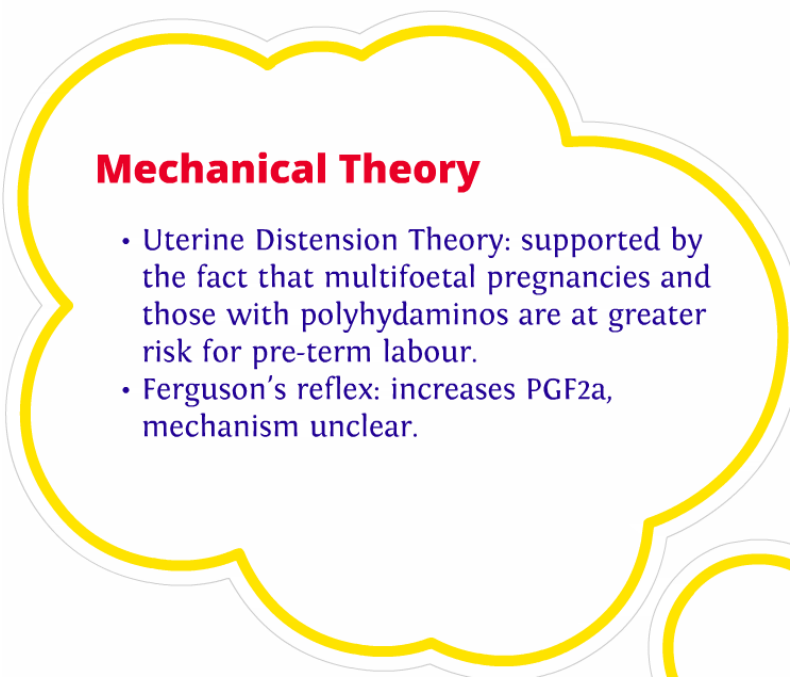
További adatok

A vázlat látható.

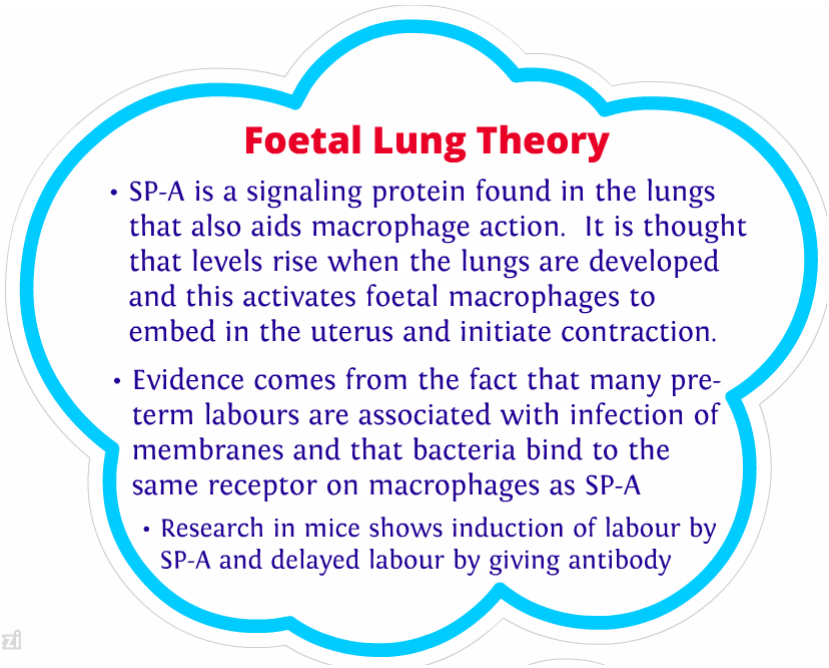
A KÉRDÉSKRE ADHATÓ VÁLASZOK

Hogy mi indítja be a szülést,

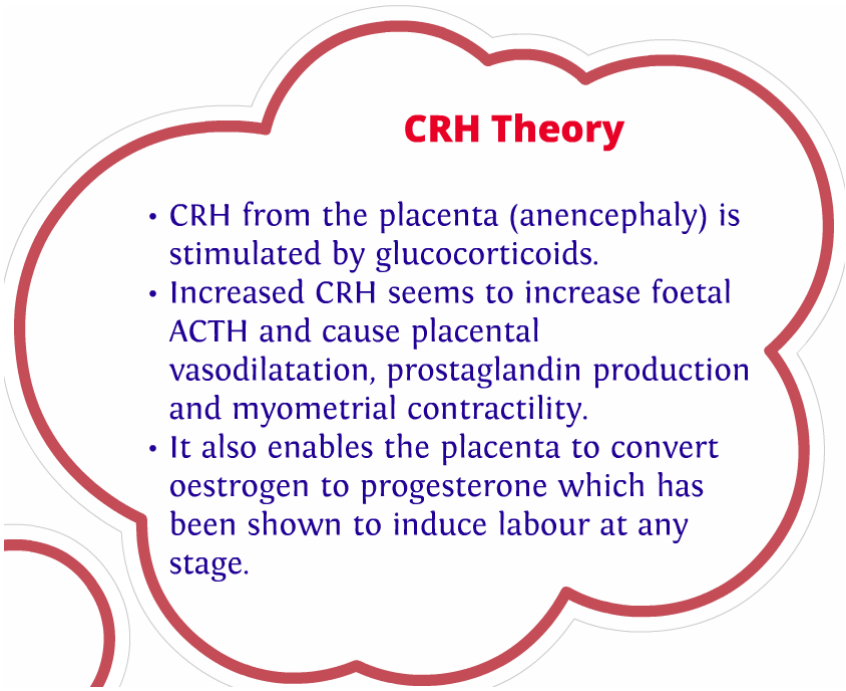
három fontosabb magyarázat említhető.



A mechanikus: a méh feszülése, a Ferguson reflex alapján.



A magzati tüdő: felszínaktív anyagának fehérjéje (Surface Protein-A) jelátvivő is egyben és a makrophagokat aktiválja a magzatburkok fertőzése, koraszülés során. A baktériumok a makrophagoknak ugyanazon felszíni receptorához kötődnek, mint az SP-A. Egerekben SP-A-val a szülés indukálható, antitest adásával viszont késleltethető.



A Cortocotropin Releasing Hormone fokozott placentáris termelődése vasodilalatiót, prostaglandin termelést és myometrium kontraktilitást eredményez.

Hogy miért pont 40 hét múlva? - A szülés megindulásának titkai

Máriáss Márta

Forrás: hazipatika.com
2008. március 8. | Frissítve: 2015. augusztus 9.

Hogy mi váltja ki a szülés megindulását, egyelőre nem ismert pontosan, de néhány történésben már biztosak lehetünk.

Méretes és érett baba, egyre több ösztrogén hormon
A szülés időpontját a baba érettsége, fejlettsége is befolyásolja.
A fejlett magzat által kibocsátott hormonok is hatnak a méhlepényre, a méhlepény anyagai, enzimei pedig az anyai ösztrogén-, adrenalin- és noradrenalin hormon termelését fokozzák, majd pedig ezek visszahatnak a magzat hormonháztartására, érésére.

Itt is, ott is gyűlik az oxitocin
A fájások helye - előkészületek a méhizomzatban
Idegek és hormonok unszolása
Időjárás és egyéb bizonytalan tényezők

Ahogy sejtettük is, nyoma sincs egyfajta biológiai gongütésnek, melynek egyértelmű hangjára hirtelen beindul a szülés. A baba és a mama testének párbeszéde, környezetük jeleinek értékelése nyomán együttes döntés eredménye a szülés megindulása, mely óvatosan, apránként veszi kezdetét, mintha csak anya és gyermeke együtt figyelnék, alkalmas-e az idő a nagy pillanatra, s készen állnak, hogy bármely pillanatban beavatkozzanak, leálljanak, vagy gyorsítsák a csoda lezajlását, az új élet születését.

A főbb tényezők, „neuroendokrin” okok: pl. ösztrogén túlsúly, oxitocin hatás. A kissé szépirodalmi megfogalmazású záró bekezdést érdemes elolvasni.

Ignoramus et ignorabimus

The Latin maxim ***ignoramus et ignorabimus***, meaning "we do not know and will not know", stood for a position on the limits of scientific knowledge, in the thought of the nineteenth century. It was given credibility by Emil du Bois-Reymond, a German physiologist, in his *Über die Grenzen des Naturerkennens* ("On the limits of our understanding of nature") of 1872.

Emil du Bois-Reymond (1818-1896)

Hilbert's reaction

David Hilbert suggested that such a conceptualization of human knowledge and ability is extremely pessimistic. We can find answers to many of these questions, and by considering them unsolvable, we limit our understanding. In 1900, in an address to the International Congress of Mathematicians in Paris, Hilbert suggested that answers to the problems of mathematics are possible with human effort. He declared that, "In mathematics there is no *ignorabimus*."
„We must not believe those, who today, with philosophical bearing and deliberative tone, prophesy the fall of culture and accept the *ignorabimus*. For us there is no *ignorabimus*, and in my opinion none whatever in natural science. In opposition to the foolish *ignorabimus* our slogan shall be: *Wir müssen wissen — wir werden wissen.* ('We must know - we will know.')”

David Hilbert

A természettudományos megismerésnek határai vannak. Du Bois Reymond, a neves német élettanász – többek közt az akciós potenciál felfedezője! – egyenesen agnoszticizmusba hajlik: „nem ismerjük és nem is fogjuk megismerni”. Egyik ellenfele, a matematikus Hilbert nézőpontja viszont: ”tudnunk kell és tudni is fogjuk”.

Physiology of parturition

Errol R Norwitz, MD, PhD

Parturition cascade — It is likely that a "parturition cascade" exists at term which removes the mechanisms maintaining uterine quiescence and recruits factors promoting uterine activity. Given its teleological importance, such a cascade would likely have multiple redundant loops to ensure a fail-safe system of securing pregnancy success (and thus preserving 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 suggest that **it may not be possible to single out any one signaling mechanism** as being responsible for the initiation of labor. Therefore, it is prudent to describe such mechanisms as being responsible for **"promoting",** rather than **"initiating",** the process of labor.

Témánk megismerése szempontjából fontos, hogy
● a szülés egy eseménysorozat, történések láncolata, szabályozott lépésekkel,
●egyetlen mechanizmust helytelen kiemelni: célszerű előmozdító-t , „promoting” megjelölni a beindító, „initiating” helyett.

The Scientist
May 2013 Issue

Why So Soon?

Researchers are using modern experimental tools to probe the mysterious molecular pathways that lead to premature labor and birth.

By Bob Grant | May 1, 2013

Ami pedig a koraszülöttséget, a koraszülést illeti, lényeges, hogy a kutatók ennek titokzatos, molekuláris útvonalait próbálják felderíteni.

Science. 2014 Aug 15;345(6198):760-5.

Preterm labor: one syndrome, many causes.

Romero R, Dey SK, Fisher SJ.

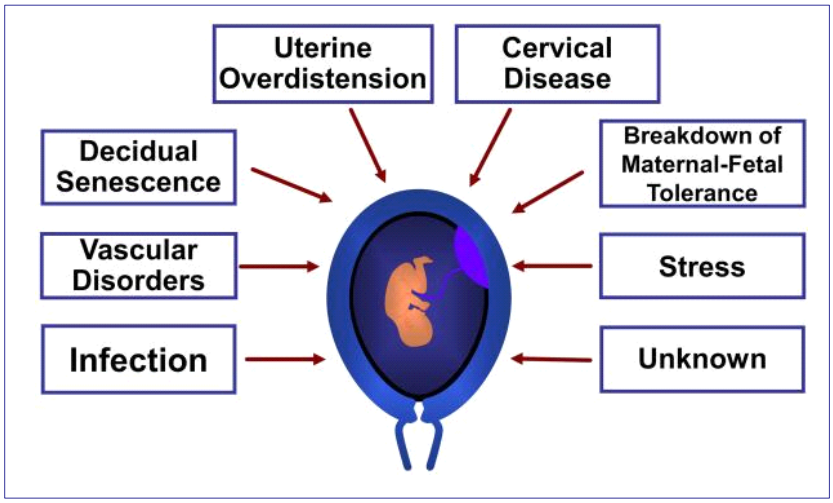
Abstract

Preterm birth is associated with 5 to 18% of pregnancies and is a leading cause of infant morbidity and mortality. Spontaneous preterm labor, a syndrome caused by multiple pathologic processes, leads to 70% of preterm births. The prevention and the treatment of preterm labor have been long-standing challenges.

We summarize the current understanding of the mechanisms of disease implicated in this condition and review advances relevant to intra-amniotic infection, decidual senescence, and breakdown of maternal-fetal tolerance.

The success of progestogen treatment to prevent preterm birth in a subset of patients at risk is a cause for optimism. Solving the mystery of preterm labor, which compromises the health of future generations, is a formidable scientific challenge worthy of investment.

Maga a koraszülés egy szindróma, sokféle okkal – amint a Science taglalja.



Proposed mechanisms of disease implicated in spontaneous preterm labor. Genetic and environmental factors are likely contributors to each mechanism.

A spontán koraszüléshez vezető kórállapotok, mechanizmusok létrejöttében genetikai és környezeti tényezők egyaránt szerepelhetnek. Kiemelendő a fertőzés és a stressz szerepe, de vannak ismeretlen mozzanatok is.

In Vivo. 2012 Sep-Oct;26(5):799-812.

Review: Impact of mediators present in amniotic fluid on preterm labour.
Vrachnis N et al.

Abstract
Preterm birth continues to be one of the most important issues in current obstetric medicine, being the single largest cause of perinatal morbidity and mortality. The signals that initiate preterm and term labour remain a mystery. Intrauterine inflammation with the secretion of cytokines is one of the accepted explanations for the mechanism of initiation of preterm labour. This review discusses the current understanding of the molecular mechanisms for the initiation of preterm labour, focusing chiefly on the role of intra-amniotic fluid mediators, whether endogenous or infection-induced, in the regulation of inflammatory response pathways associated with spontaneous preterm labour. Prostaglandins (PGs) are considered to be one of the key mediators of preterm labour, with the concentration of biologically active PGs in the amniotic fluid, particularly PGE(2) and PGF(2α), being significantly higher in women with preterm labour. Cytokines, such as interleukins and tumour necrosis factor alpha, additionally play a dominant role in preterm labour, particularly in association with infection. Elevated amniotic fluid concentrations of extracellular matrix mediators, including metalloproteases, are also implicated in the process of foetal membrane rupture in preterm labour. Allelic variations in the main amniotic fluid mediators may be the key to understanding the disparity in the rates of preterm birth between different ethnic populations. We also discuss the role of other potential mediators such as cell-adhesion molecules, nitric oxide and novel biomarkers found in the amniotic fluid.

Hatalmas áttekintő közlemény tárgyalja az amnion folyadékban kimutatható mediátorok (pl. prosztaglandinok, cytokinek, metalloproteinázok és egyéb biomarkerek) szerepét a koraszülésben, hangsúlyozva a méhen belüli gyulladás, a cytokinek jelentőségét.

J Leukoc Biol. 2016 Jan;99(1):67-78.

Inflammation and preterm birth.

Cappelletti M et al.

Abstract

Preterm birth is the leading cause of neonatal morbidity and mortality. Although the underlying causes of pregnancy-associated complication are numerous, it is well established that infection and inflammation represent a highly significant risk factor in preterm birth. However, despite the clinical and public health significance, infectious agents, molecular trigger(s), and immune pathways underlying the pathogenesis of preterm birth remain underdefined and represent a major gap in knowledge. Here, we provide an overview of recent clinical and animal model data focused on the interplay between infection-driven inflammation and induction of preterm birth. Furthermore, here, we highlight the critical gaps in knowledge that warrant future investigations into the interplay between immune responses and induction of preterm birth.

A fertőzés és a gyulladás a koraszülésnek fontos kockázati tényezői, ámde a fertőző ágensekre, a molekuláris triggerekre, az immunválasz útvonalaira vonatkozó ismereteink még hiányosak (2016).

Ann N Y Acad Sci. 2005 May;1041:345-50.

Mechanisms of relaxin-mediated premature birth.

Weiss G, Goldsmith LT.

Abstract
In women, circulating relaxin is produced by the corpus luteum of pregnancy. The levels of relaxin are predominantly determined by the luteal mass, the number of corpora lutea present. Relaxin levels are highest after ovulation induction, which stimulates formation of many corpora lutea. Elevated relaxin levels in the first trimester of pregnancy are maintained throughout pregnancy and are linearly related to preterm birth. In an in vitro model of late human pregnancy cervix, relaxin increases MMP-1 and MMP-3 and decreases TIMP-1 levels, thus acting as a positive regulator of matrix metalloproteinases. In an in vivo rhesus monkey model of early pregnancy, relaxin decreases cervical collagen content, decreases cervical lumican levels, and stimulates MMP-7 levels. Early effects of relaxin in the uterus include increasing endometrial arteriole number and increasing the number of leukocytes, uterine natural killer cells, macrophages, and neutrophils. These cells release many cytokines which contribute to changes that stimulate and facilitate uterine contractility. If these changes persist in late pregnancy, relaxin may be a mediator of labor. Excess relaxin may produce these changes at an accelerated rate, causing preterm birth.

Elég régen ismert a relaxin szerepe a koraszülésben (pl. a méhnyak metalloproteinázai, a méh kontraktilitása) a relaxin – gyulladásos sejt infiltráció – cytokinek bonyolult útvonalon át.

Front Immunol. 2014 Nov 12;5:567.
Oxidative stress damage as a detrimental factor in preterm birth pathology.
Menon R.

Abstract
Normal term and spontaneous preterm births (PTB) are documented to be associated with oxidative stress (OS), and imbalances in the redox system (balance between pro- and antioxidant) have been reported in the maternal-fetal intrauterine compartments. The exact mechanism of labor initiation either at term or preterm by OS is still unclear, and this lack of understanding can partially be blamed for failure of antioxidant supplementation trials in PTB prevention. Based on recent findings from our laboratory, we postulate heterogeneity in host OS response. The physiologic (at term) and pathophysiologic (preterm) pathways of labor are not mediated by OS alone but by OS-induced damage to intrauterine tissues, especially fetal membranes of the placenta. OS damage affects all major cellular elements in the fetal cells, and this damage promotes fetal cell senescence (aging). The aging of the fetal cells is predominated by p38 mitogen activated kinase (p38MAPK) pathways. Senescing cells generate biomolecular signals that are uterotonic, triggering labor process. The aging of fetal cells is normal at term. However, aging is premature in PTB, especially in those PTBs complicated by preterm premature rupture of the membranes, where elements of redox imbalances and OS damage are more dominant. We postulate that fetal cell senescence signals generated by OS damage are likely triggers for labor. This review highlights the mechanisms involved in senescence development at term and preterm by OS damage and provides insight into novel fetal signals of labor initiation pathways.

Az oxidatív stressz szerepe ismert: a méhen belüli szövetek, a magzatburkok, a magzati sejtek károsodása öregedéshez (senescence, aging) vezet, az „elöregedett” sejtek biomolekoláris uterotonikus jelei váltják ki a szülést. Ez főleg a korai burokrepedéses esetekre jellemző.

Exp Physiol. 2014 Mar;99(3):525-9.
The importance of the smooth muscle cytoskeleton to preterm labour.
Morgan KG.

Abstract
Multiple mechanisms have been shown to regulate the onset of labour in a co-operative and complex manner. One factor, myometrial stretch and associated increases in wall tension, has been implicated clinically in the initiation of labour and especially the aetiology of preterm labour. Recent work on the mechanisms involved has led to the finding that the intracellular Ca(2+) requirement for activation of the myometrial contractile filaments increases during gestation. The decreased Ca(2+) sensitivity correlates with an increase in the expression of caldesmon, an actin-binding protein and inhibitor of myosin activation, during pregnancy. In late pregnancy, an increase in extracellular signal-regulated kinase-mediated caldesmon phosphorylation occurs, which appears to reverse the inhibitory action of caldesmon during labour. Force generated by the myometrial contractile filaments is communicated across the plasmalemma to the uterine wall through focal adhesions. Phospho-tyrosine screening and mass spectrometry of stretched myometrial samples identified several stretch-activated focal adhesion proteins. This Src-mediated focal adhesion signalling appears to provide a tunable, i.e. regulated, tension sensor and force transmitter in the myometrial cell. In other parallel studies, biophysical measurements of smooth muscle compliance at both the cellular and tissue levels suggest that decreases in cellular compliance due to changing interactions of the actin cytoskeleton with the focal adhesions may also promote increases in uterine wall tension. These results, taken together, suggest that focal adhesion proteins and their interaction with the cytoskeleton may present a new mode of regulation of uterine contractility.

A méhizomzat feszülése, a simaizom tenziójának fokozódása a terhesség folyamán fokozódó intracelluláris kalcium igény, a csökkent kalcium érzékenység miatt jön létre. Fokozódik ugyanakkor a Caldesmon – aktin kötő, miozin aktivációt gátló fehérje – termelődése is. A terhesség végefelé viszont a Caldesmon foszforilálódik, elveszti gátló hatását. A méhfal tenziójának fokozódásában az aktin cytoskeleton és a fokális adhéziók kölcsönhatása is szerepet játszik.

Dis Markers. 2015;2015:435014.

Predicting Preterm Labour: Current Status and Future Prospects.

Georgiou HM et al.

Abstract
Preterm labour and birth are a major cause of perinatal morbidity and mortality. Despite modern advances in obstetric and neonatal management, the rate of preterm birth in the developed world is increasing. Yet even though numerous risk factors associated with preterm birth have been identified, the ability to accurately predict when labour will occur remains elusive, whether it is at a term or preterm gestation. In the latter case, this is likely due to the multifactorial aetiology of preterm labour wherein women may display different clinical presentations that lead to preterm birth. The discovery of novel biomarkers that could reliably identify women who will subsequently deliver preterm may allow for timely medical intervention and targeted therapeutic treatments aimed at improving maternal and fetal outcomes. Various body fluids including amniotic fluid, urine, saliva, blood (serum/plasma), and cervicovaginal fluid all provide a rich protein source of putative biochemical markers that may be causative or reflective of the various pathophysiological disorders of pregnancy, including preterm labour. This short review will highlight recent advances in the field of biomarker discovery and the utility of single and multiple biomarkers for the prediction of preterm birth in the absence of intra-amniotic infection.

Praedictio: hogyan lehet a koraszülést „megjósolni”, előre jelezni?
A multifaktoriális etiológia miatt, a kockázati tényezők alig, viszont 羊 a már előbb (Vrachnis) említett és – újabb biomarkerek inkább megbízhatóak.
A testnedvekben (amnion folyadék, vizelet, nyál, vér, cervicovaginális folyadék) kimutatható biokémiai markerek a kórfolyamatoknak vagy kiváltói vagy következményei.

J Reprod Immunol. 2011 Mar;88(2):176-84.
Pharmacological inhibition of inflammatory pathways for the prevention of preterm birth.
Keelan JA

Abstract
The major cause of spontaneous preterm birth (sPTB) at less than 32 weeks of gestation is intrauterine inflammation as a consequence of colonisation of the gestational membranes by pathogenic microorganisms which trigger activation of the local innate immune system. This results in release of inflammatory mediators, leukocytosis (chorioamnionitis), apoptosis, membrane rupture, cervical ripening and onset of uterine contractions. Recent PCR evidence suggests that in the majority of cases of inflammation-driven preterm birth, microorganisms are present in the amniotic fluid, but these are not always cultured by standard techniques. The nature of the organism and its cell wall constituents, residence time in utero, microbial load, route of infection and extent of tissue penetration are all factors which can modulate the timing and magnitude of the inflammatory response and likelihood of progression to sPTB. Administration of anti-inflammatory drugs could be a viable therapeutic option to prevent sPTB and improve fetal outcomes in women at risk of intrauterine inflammation. Preventing fetal inflammation via administration of placenta-permeable drugs could also have significant perinatal benefits in addition to those related to extension of gestational age, as a fetal inflammatory response is associated with a range of significant morbidities. A number of potential drugs are available, effective against different aspects of the inflammatory process, although the pathways actually activated in spontaneous preterm labour have yet to be confirmed. Several pharmacological candidates are discussed, together with clinical and toxicological considerations associated with administration of anti-inflammatory agents in pregnancy.

A spontán koraszülés legfőbb oka a méhen belüli gyulladás, amely a magzatburkok kolonizációjának a következménye: a kórokozók, melyek a lokális, veleszületett immunrendszert aktiválják PCR-rel kimutathatók. Prevenció céljára anti-inflammatorikus gyógyszerek alkalmazhatók.

TOVÁBBI ADATOK

Can Med Assoc J. 1983 Feb 15;128(4):387-92.

Initiation of parturition in humans.

Drover JW, Casper RF.

Abstract
The mechanism by which parturition is initiated in humans is largely unknown. The placenta and fetal membranes appear to play the major role in the initiation of labour, and the fetus may influence the timing of labour. Clinical observations and experiments with animals have revealed that placental neuropeptides may be able to control steroid metabolism and trigger the onset of labour, while the fetus may be able to interact with such events to initiate parturition at an appropriate time. However, further study is needed to determine the role of placental releasing factors and glycoprotein hormones and their ability to control placental steroid metabolism.

Az első nagyobb összefoglaló (1983) az endokrin tényezők szerepét hangsúlyozza. Rámutat a placenta, a magzatburkok, illetve magának a magzatnak a szerepére, valamint ezek kölcsönhatására, összjátékára.

Az ezt követő fejlődés főbb mérföldkövei:

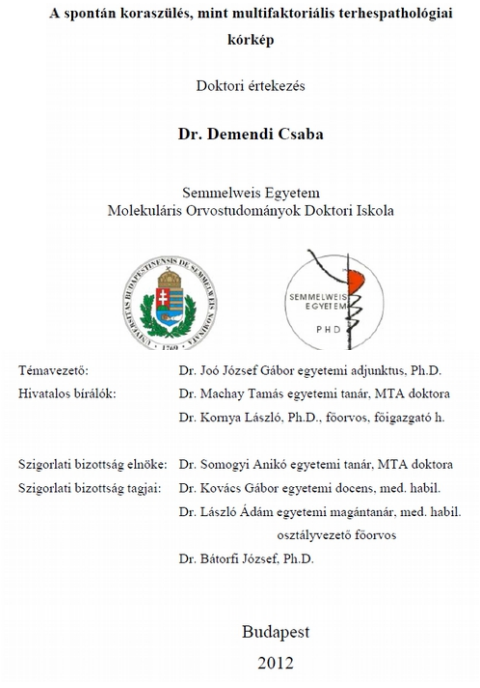
Ann Med. 2008;40(3):167-95.

Genetic contributions to preterm birth: implications from epidemiological and genetic association studies.

Plunkett J, Muglia LJ.

Abstract
Infants born before term (<37 weeks) have an increased risk of neonatal mortality as well as other health problems. The increasing rate of preterm birth in recent decades, despite improvements in health care, creates an impetus to better understand and prevent this disorder. Preterm birth likely depends on a number of interacting factors, including genetic, epigenetic, and environmental risk factors. Genetic studies may identify markers, which more accurately predict preterm birth than currently known risk factors, or novel proteins and/or pathways involved in the disorder. This review summarizes epidemiological and genetic studies to date, emphasizing the complexity of genetic influences on birth timing. While several candidate genes have been reportedly associated with the disorder, inconsistency across studies has been problematic. More systematic and unbiased genetic approaches are needed for future studies to examine the genetic etiology of human birth timing thoroughly.

Évtizedek során előtérbe került az egymással kölcsönhatásban működő genetikai, epigenetikai, valamint környezeti kockázati tényezők jelentősége. A komplex hatások kutatása során számos, további vizsgálatot igénylő bizonytalanság is felmerült



A spontán koraszülés, mint multifaktoriális terhespathológiai kórkép

Doktori értekezés

Dr. Demendi Csaba

Semmelweis Egyetem
Molekuláris Orvostudományok Doktori Iskola

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	Dr. László Ádám egyetemi magántanár, med. habil. osztályvezető főorvos
	Dr. Bátorfi József, Ph.D.

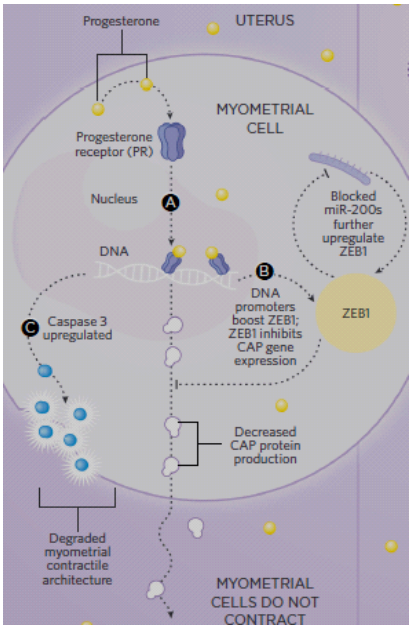
Budapest
2012

Hazai vonatkozásban említendő Demendi értekezése a multifaktoriális spontán koraszülésről – ismerős nevekkel a címoldalon.

MOLECULAR MODELS OF BIRTH

MAINTAINING PREGNANCY

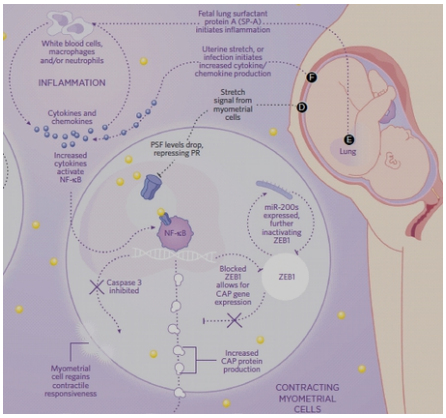
Progesterone interacts with progesterone receptors (PRs) in the cytoplasm of myometrial cells, causing the complex to translocate to the nucleus ν
A . There, the activated receptor binds to the promoter of the ZEB1 gene, which leads to upregulation of the transcription factors and subsequent inhibition of genes that code for contraction-associated proteins (CAPs) ν
B . PRs in the nucleus also upregulate caspase 3, an enzyme that degrades the contractile architecture of the cell ν
C . All of this results in a quiescent uterus that is allowed to stretch and grow as the fetus develops.



A szülés molekuláris modelljei közül először a terhesség fenntartásának útvonalai:
● progeszteron, progeszteron receptor, ennek hatása a ZEB1 génre, majd a kontrakcióhoz társuló fehérjék (CAPs) gátlása,
● a caspase 3 „felszabályozása”, így a kontraktilitási architektúra „lebontása”,
● mindezekkel: az uterus nyugalomban marad.

MOLECULAR MODELS OF BIRTH

INITIATING LABOR
Mechanical stretch forces in the uterus cause a drop in polypyrimidine tract binding protein-associated splicing factor (PSF), a coregulator of the progesterone receptor. This leads to the increased expression of proteins involved in contraction
D. As the fetal lung matures, it produces an abundance of surfactant protein A (SP-A), which activates macrophages in the amniotic fluid, promoting their migration to the uterus where they release proinflammatory cytokines. Increased cytokine production activates NF-κB, which translocates to the nucleus of the myometrial cell, where it binds to CAP gene promoters, activating CAP expression. It also binds to PRs, blocking their binding with DNA. This decreases ZEB1 expression, therefore increasing expression of CAPs and decreasing caspase 3 levels
E . Signals from uterine stretch forces and intraamniotic infection can also increase proinflammatory cytokines and chemokines, which can result in increased CAP expression and the start of labor
F . Other hormones, such as prostaglandins, contact their receptors in the membranes of myometrial cells, causing an influx of Ca2+and uterine muscle contractions.



A szülés beindítása: miként a méh „feszülése” és a magzati tüdő SP-A aktivitása is, bonyolult útvonalon át,
● a CAP expresszió fokozódása és
● a caspase 3 szint csökkenéséhez vezet;
● a prosztaglandinok receptorhoz való kötődése a myometrium sejtjeibe calcium beáramlást s így méhizom kontrakciót okoz
● mindezek együttes hatására a szülés beindul.

Cold Spring Harb Perspect Med. 2015 Sep 3;5(11).

Molecular Regulation of Parturition: A Myometrial Perspective.
Renthal NE et al.

Abstract
The molecular mechanisms that maintain quiescence of the myometrium throughout most of pregnancy and promote its transformation to a highly coordinated contractile unit culminating in labor are complex and intertwined. During pregnancy, progesterone (P4) produced by the placenta and/or ovary serves a dominant role in maintaining myometrial quiescence by blocking proinflammatory response pathways and expression of so-called "contractile" genes. In the majority of **placental mammals**, increased uterine contractility near term is heralded by an increase in circulating estradiol-17β (E2) and/or increased estrogen receptor α (ERα) activity and a sharp decline in circulating P4 levels. However, in **women**, circulating levels of P4 and progesterone receptors (PR) in myometrium remain elevated throughout pregnancy and into labor. This has led to the concept that increased uterine contractility leading to term and preterm labor is mediated, in part, by a decline in PR function. The biochemical mechanisms for this decrease in PR function are also multifaceted and interwoven. In this paper, we focus on the molecular mechanisms that mediate myometrial quiescence and contractility and their regulation by the two central hormones of pregnancy, P4 and estradiol-17β. The integrative roles of microRNAs also are considered.

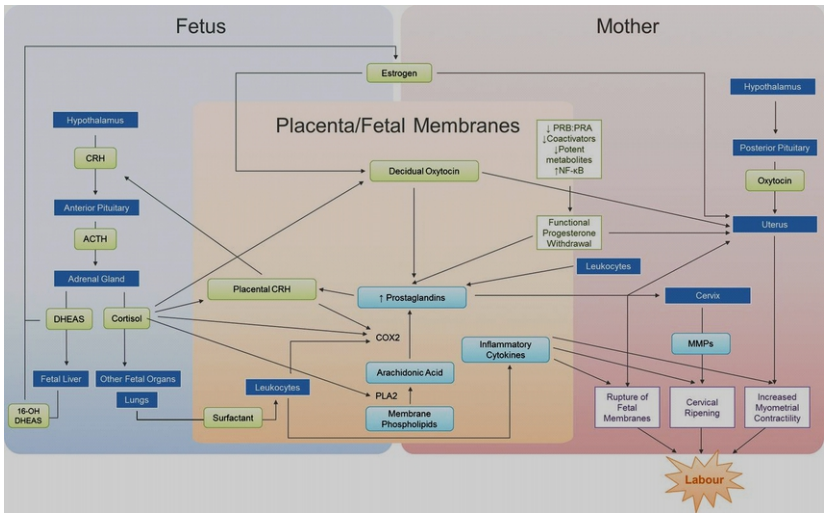
A progeszteron (P4) a myometrium nyugalmi állapotáért felel. Emlősökben a keringő ösztradiol (E2) és receptorának (ERα) aktiválása a P4 szint csökkenésével, a méh kontraktilitás fokozódásával jár. Terhes nőkben viszont aP4 és a progeszteron receptor (PR) emelkedett marad, így a PR funkció csökkenésével kell számolnunk, s ez (kora)szüléshez vezet.

Mol Hum Reprod. 2013 Nov;19(11):711-7.
Computer models to study uterine activation at labour.
Sharp GC, Saunders PT, Norman JE.

Abstract
Improving our understanding of the initiation of labour is a major aim of modern obstetric research, in order to better diagnose and treat pregnant women in which the process occurs abnormally. In particular, increased knowledge will help us identify the mechanisms responsible for preterm labour, the single biggest cause of neonatal morbidity and mortality. Attempts to improve our understanding of the initiation of labour have been restricted by the inaccessibility of gestational tissues to study during pregnancy and at labour, and by the lack of fully informative animal models. However, computer modelling provides an exciting new approach to overcome these restrictions and offers new insights into uterine activation during term and preterm labour. Such models could be used to test hypotheses about drugs to treat or prevent preterm labour. With further development, an effective computer model could be used by healthcare practitioners to develop personalized medicine for patients on a pregnancy-by-pregnancy basis. Very promising work is already underway to build computer models of the physiology of uterine activation and contraction. These models aim to predict changes and patterns in uterine electrical excitation during term labour. There have been far fewer attempts to build computer models of the molecular pathways driving uterine activation and there is certainly scope for further work in this area. The integration of computer models of the physiological and molecular mechanisms that initiate labour will be particularly useful.

Anyai szövetmintákhoz nehéz hozzáférni , és állatmodellek sincsenek, ezért a méh aktivációja és kontrakciója, ezek molekuláris mechanizmusai komputeres modellekben tanulmányozhatók.

Key endocrine and inflammatory factors associated with the initiation of human parturition.



G.C. Sharp et al. Mol. Hum. Reprod. 2013;19:711-717

MHR
Basic science of reproductive medicine

Az ábra a szülés beindulásában szereplő főbb gyulladásos és endokrin tényezőket mutatja be a magzatban, a placentában – magzatburkokban és az anyában:
● surfactant ●oxytocin, CRH ● cytokinek, MMPk

Clin Perinatol. 1993 Mar;20(1):9-28.

Biologic basis of term and preterm labor.

Myers DA1, Nathanielsz PW.

Abstract
Normal parturition in **sheep and nonhuman primates** appears to be initiated by signals from the fetus. These signals involve the fetal hypothalamo-hypophyseal-adrenal axis and are closely integrated with the control of maturation of the fetal organs such as the lungs, gut, and kidneys that are indispensable for extrauterine life. The integrated set of changes in fetal and maternal myometrial, decidual, and cervical tissues are gradual and occur over several days. When the myometrium and cervix have been appropriately prepared, endocrine and paracrine factors in the fetal membranes, decidua, and the myometrium bring about a change in the pattern of myometrial activity from contractures to contractions. This switch occurs at night, and recurs and augments over several nights until eventually cervical dilation occurs to allow the fetus to be born.

A koraszülés biológiai alapjai: állatokban a magzati szignálok, a szövetek érése, a magzati és anyai szövetek integrált változása, „előkészítése” végül is a magzatburkokban, a myometriumban ható endokrin és parakrin tényezők révén vezet myometrium kontrakciókhoz.

Gynecol Endocrinol. 2015;31(9):679-83.

Factors implicated in the initiation of human parturition in term and preterm labor: a review.

Ravanos K et al.

Abstract
After accommodating the pregnancy for an average of 40 weeks, the uterus expels the fetus, the placenta and the membranes through the birth canal in a process named parturition. The absolute sequence of events that trigger and sustain **human** parturition are not yet fully clarified. Evidence suggests that spontaneous preterm and term labor seem to share a common inflammatory pathway. However, there are several other factors being involved in the initiation of human parturition. Placental corticotropin releasing hormone production seems to serve as a placental clock that might be set to ring earlier or later determining the duration of pregnancy and timing of labor. Estrogens do not cause contractions but their properties seem to capacitate uterus to coordinate and enhance contractions. Cytokines, prostaglandins, nitric oxide and steroids seem also to induce ripening by mediating remodeling of the extracellular matrix and collagen. Infection and microbe invasion resulting in chorioamnionitis also represents a common cause of early preterm labour. This review provides an overview of all these factors considered to be implicated in the initiation of human parturition.

Emberben mindez máig nem eléggé ismert. A számos tényező közül kiemelendő a gyulladásos útvonal, valamint a placenta CRH-ja, a „placentáris óra”. A cytokinek, prosztaglandinok és egyebek mellet a fertőzés a chorioamnitishez vezető baktérium invázió a koraszülés gyakori oka.

BJOG. 2003 Apr;110 Suppl 20:39-45.
Mechanisms of labour – biochemical aspects.
López Bernal A

Abstract
The mechanism of labour is not fully understood and further research into this important physiological process is needed. In some species, notably sheep, parturition is due to activation of the fetal hypothalamic-pituitary-adrenal axis. However, in primates, this axis appears to have a supportive, rather than essential role. Successful parturition requires an increase in coordinated uterine contractility together with changes in connective tissue that allow cervical ripening and dilatation. In most mammals, however, these changes are synchronised by a fall in maternal progesterone levels and a rise in oestrogens. This is not the case in women in whom the onset of labour occurs without apparent changes in circulating steroid levels.
The basis of uterine contractility is the interaction between actin and myosin in myometrial smooth muscle cells. This is driven by **calcium** through Ca(2+)-calmodulin-dependent myosin light chain kinase (MLCK) activity. Moreover, calcium sensitisation occurs via activation of Rho kinase, a calcium-independent pathway that promotes contractility by inhibiting myosin phosphatase and probably by phosphorylating myosin on the same site as MLCK.
Uterine activity can be modulated by many G-protein coupled receptors (GPCRs). For example,
receptors coupled to Galpha(q) (oxytocin-, prostanoid FP and TP, endothelin-receptors) stimulate contractility by activating the phospholipase C/Ca(2+) pathway;
receptors coupled to Galpha(s) (beta(2)-adrenoceptors, prostanoid EP2 and IP, some 5-hydroxytryptamine receptors e.g. 5-HT(7)) relax the uterus by increasing myometrial cyclic AMP levels; and
receptors coupled to Galpha(i) (alpha(2)-adrenoceptors, muscarinic, 5-HT(1)) potentiate contractility, probably by inhibiting cAMP production.
Because of its relative abundance in pregnant uterine tissue, the oxytocin receptor is an obvious target for tocolytic therapy. Oxytocin antagonists have been introduced into clinical practice for the management of preterm labour and offer the advantage of uterine selectivity and fewer side effects than conventional beta-agonist therapy.

A méhizomzat kontraktilitásában, a biokémiai folyamatok közül, az aktin és miozin kölcsönhatása fontos, melyet a kalcium-hatással kapcsolatos miozin könnyű lánc kináz (MLCK), valamint számos G-proteinhez kapcsolt receptor (GPCR) modulál: serkent vagy gátol.

Hormones (Athens). 2012 Oct-Dec;11(4):397-409.
Endocrine, paracrine, and autocrine placental mediators in labor.
Iliodromiti Z et al.

Abstract
Considering that preterm birth accounts for about 6-10% of all births in Western countries and of more than 65% of all perinatal deaths, elucidation of the particularly complicated mechanisms of labor is essential for determination of appropriate and effective therapeutic interventions. Labor in humans results from a complex interplay of fetal and maternal factors, which act upon the uterus to trigger pathways leading gradually to a coordinated cervical ripening and myometrial contractility. Although the exact mechanism of labor still remains uncertain, several components have been identified and described in detail. Based on the major role played by the human placenta in pregnancy and the cascade of labor processes activated via placental mediators exerting endocrine, paracrine, and autocrine actions, this review article has aimed at presenting the role of these mediators in term and preterm labor and the molecular pathways of their actions. Some of the aforementioned mediators are involved in myometrial activation and preparation and others in myometrial stimulation leading to delivery. In the early stages of pregnancy, myometrial molecules, like progesterone, nitric oxide, and relaxin, contribute to the retention of pregnancy. At late stages of gestation, fetal hypothalamus maturation signals act on the placenta causing the production of hormones, including CRH, in an endocrine manner; the signals then enhance paracrinically the production of more hormones, such as estrogens and neuropeptides, that contribute to cervical ripening and uterine contractility. These molecules act directly on the myometrium through specific receptors, while cytokines and multiple growth factors are also produced, additionally contributing to labor. In situations leading to preterm labor, as in maternal stress and fetal infection, cytokines trigger placental signaling sooner, thus leading to preterm birth.

A szülési folyamat komplex magzati és anyai tényezők együttesének eredője, a méhnyak „érésén” és a myometrium kontraktilitásán át; a terhesség késői stádiumában endokrin és parakrin hatások eredményezik ezt.
A bonyolult placentáris „jeladás” (signaling) pl. anyai stressz, illetve magzati fertőzés esetében a cytokin hatás miatt korábban lép fel, s így vezet koraszüléshez.

Endocrinology of Pregnancy.

Tal R, et al.

Endotext [Internet]. South Dartmouth (MA): 2015 Dec 7.

Physiology of parturition

Errol R Norwitz, MD, PhD

http://www.uptodate.com 2016 UpToDate

A terhesség endokrinológiáját, illetve élettanát két terjedelmes, alapos, modern összefoglaló tárgyalja.

Proc Natl Acad Sci U S A. 2004 Apr 6;101(14):4978-83.

Surfactant protein secreted by the maturing mouse fetal lung acts as a hormone that signals the initiation of parturition.

Condon JC et al.

Abstract
Parturition is timed to begin only after the developing embryo is sufficiently mature to survive outside the womb. It has been postulated that the signal for the initiation of parturition arises from the fetus although the nature and source of this signal remain obscure. Herein, we provide evidence that this signal originates from the maturing fetal lung. In the mouse, secretion of the major lung surfactant protein, surfactant protein A (SP-A), was first detected in amniotic fluid (AF) at 17 days postcoitum, rising progressively to term (19 days postcoitum). Expression of IL-1beta in AF macrophages and activation of NF-kappaB in the maternal uterus increased with the gestational increase in SP-A. SP-A stimulated IL-1beta and NF-kappaB expression in cultured AF macrophages. Studies using Rosa 26 Lac-Z (B6;129S-Gt(rosa)26Sor) (Lac-Z) mice revealed that fetal AF macrophages migrate to the uterus with the gestational increase in AF SP-A. Intraamniotic (i.a.) injection of SP-A caused preterm delivery of fetuses within 6-24 h. By contrast, injection of an SP-A antibody or NF-kappaB inhibitor into AF delayed labor by >24 h. We propose that augmented production of SP-A by the fetal lung near term causes activation and migration of fetal AF macrophages to the maternal uterus, where increased production of IL-1beta activates NF-kappaB, leading to labor. We have revealed a response pathway that ties augmented surfactant production by the maturing fetal lung to the initiation of labor. We suggest that SP-A secreted by the fetal lung serves as a hormone of parturition.

A munkacsoport beszámolóból kiderül, hogy a szülés beindulásáért (egérben) a magzati tüdő felületaktív fehérjéje, mint hormon, felelős. Ennek termelődésével párhuzamosan fokozódik az NF-kappaB aktiváció a méhben. SP-A intraamniális injekciójával koraszülést lehetett kiváltani, viszont SP-A antitesttel, illetve az NF-kappaB gátlásával a szülés késleltethető.

Mol Endocrinol. 2009 Jul;23(7):947-54.

Minireview: fetal-maternal hormonal signaling in pregnancy and labor.

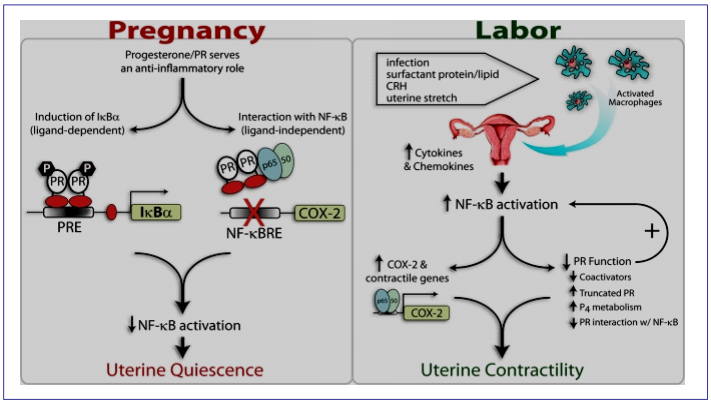
Mendelson CR

Abstract
Mechanisms underlying the initiation of parturition remain unclear. Throughout most of pregnancy, uterine quiescence is maintained by elevated progesterone acting through progesterone receptor (PR). Although in most mammals, parturition is associated with a marked decline in maternal progesterone, in humans, circulating progesterone and uterine PR remain elevated throughout pregnancy, suggesting a critical role for functional PR inactivation in the initiation of labor. Both term and preterm labor in humans and rodents are associated with an inflammatory response. In preterm labor, intraamniotic infection likely provides the stimulus for increased amniotic fluid interleukins and migration of inflammatory cells into the uterus and cervix. However, at term, the stimulus for this inflammatory response is unknown. Increasing evidence suggests that the developing fetus may produce physical and hormonal signals that stimulate macrophage migration to the uterus, with release of cytokines and activation of inflammatory transcription factors, such as nuclear factor kappaB (NF-kappaB) and activator protein 1 (AP-1), which also is activated by myometrial stretch. We postulate that the increased inflammatory response and NF-kappaB activation promote uterine contractility via 1) direct activation of contractile genes (e.g. COX-2, oxytocin receptor, and connexin 43) and 2) impairment of the capacity of PR to mediate uterine quiescence. PR function near term may be compromised by direct interaction with NF-kappaB, altered expression of PR coregulators, increased metabolism of progesterone within the cervix and myometrium, and increased expression of inhibitory PR isoforms. Alternatively, we propose that uterine quiescence during pregnancy is regulated, in part, by PR antagonism of the inflammatory response.

A munkacsoport vezetője összefoglalja a terhesség és a szülés kapcsán fellépő magzat-anyai hormonális jelátvitel szerepét A fokozott gyulladásos válaszreakció elősegíti a méhizomzat kontraktilitását

- **a kontraktilitási gének direkt aktiválásával és**
- **a progeszteron receptor (PR) „kapacitásának" károsításával.**

Más szavakkal: a méh nyugalmi állapotát („uterine quiescence”), a terhesség folyamán, a PR és a gyulladásos válaszreakció antagonizmusa határozza meg.



Mechanisms for progesterone/PR regulation of uterine quiescence during pregnancy and induction of uterine contractility in preterm and term labor. During most of pregnancy, the uterus is maintained in a quiescent state by the PR, which acts in a ligand-dependent and -independent manner to block activation of the inflammatory transcription factors (*e.g.* NF-κB). PR acts in a ligand-dependent manner to up-regulate expression of the NF-κB inhibitor IκBα in myometrial cells. Alternatively, PR acts in a dominant ligand-independent manner (likely via direct protein-protein interaction) to block NF-κB activation, DNA binding, and transactivation of contractile genes within the uterus. Labor can be initiated preterm as a result of bacterial infection, resulting in enhanced migration of macrophages to the maternal uterus with release of cytokines/chemokines and activation of NF-κB. However, at term, enhanced macrophage activation and migration and increased uterine NF-κB activity are likely induced by signals produced by the maturing fetus. These include increased secretion of surfactant proteins and lipids by the fetal lung into amniotic fluid, augmented production of CRH by the placenta, and enhanced uterine stretch caused by the growing conceptus. Within the uterus, the activated NF-κB directly acts to increase expression of contractile genes and causes an impairment of PR function by effecting 1) down-regulation of PR coactivators, 2) increased expression of inhibitory PR isoforms, 3) increased metabolism of progesterone to inactive products, and possibly 4) direct inhibitory interaction with PR. These concerted events culminate in a further increase in NF-κB activation and expression of contractile genes, leading to labor.

Az előbbieket az ábra szemlélteti.

Mol Endocrinol. 2012 Nov;26(11):1857-67.
The microRNA (miR)-199a/214 cluster mediates opposing effects of progesterone and estrogen on uterine contractility during pregnancy and labor.
Williams KC et al.
Abstract
Progesterone (P(4)) and estradiol-17β (E(2)) play critical and opposing roles in regulating myometrial quiescence and contractility during pregnancy and labor. Although these contrasting hormonal effects are likely mediated via differential regulation of inflammatory and contractile genes, the underlying mechanisms remain incompletely understood. Recently we discovered that targets of the microRNA (miR)-200 family, transcription factors zinc finger E-box binding homeobox (ZEB)-1 and ZEB2, serve as P(4)/progesterone receptor-mediated regulators of uterine quiescence during pregnancy. In the present study, we found that levels of the clustered miRNAs, miR-199a-3p and miR-214, were significantly decreased in laboring myometrium of pregnant mice and humans and in an inflammatory mouse model of preterm labor, whereas the miR-199a-3p/miR-214 target, cyclooxygenase-2, a critical enzyme in synthesis of proinflammatory prostaglandins, was coordinately increased. Overexpression of miR-199a-3p and miR-214 in cultured human myometrial cells inhibited cyclooxygenase-2 protein and blocked TNF-α-induced myometrial cell contractility, suggesting their physiological relevance. Notably, E(2) treatment of ovariectomized mice suppressed, whereas P(4) enhanced uterine miR-199a-3p/214 expression. Intriguingly, these opposing hormonal effects were mediated by ZEB1, which is induced by P(4), inhibited by E(2) and activates miR199a/214 transcription. Together, these findings identify miR-199a-3p/miR-214 as important regulators of myometrial contractility and provide new insight into strategies to prevent preterm birth.

A progeszteron (P4) – ösztrogén (E2) antagonizmus a cink ujj E-box kötő (ZEB1) transzkripciós faktorral függ össze: P4 indukálja, E2 gátolja. Maga a ZEB1 aktiválja a vizsgált miRNS – 199a/214 – transzkripciót,

- **amely viszont csökkent a szülő (laboring) myometriumban,**
- **a miR célpontjának, a ciklooxigenáz 2 enzimnek az aktivitása pedig fokozódik.**
- **Ezek alapján a miR 199/214 a méhizom kontraktilitás fontos regulátora.**

Nat Rev Endocrinol. 2013 Jul;9(7):391-401.

MicroRNAs--mediators of myometrial contractility during pregnancy and labour.
Renthal NE, Williams KC, Mendelson CR.

Abstract
The maintenance of myometrial quiescence and initiation of contractility, which lead to parturition at term and preterm, involve a shifting equilibrium between anti-inflammatory and proinflammatory signalling pathways. Progesterone (P4), acting through the progesterone receptor (PR), has an essential and multifaceted role in the maintenance of myometrial quiescence. This effect of P4-PR signalling is mediated, in part, by its anti-inflammatory actions and capacity to repress the expression of genes that encode proinflammatory cytokines, such as IL-1 and IL-6, and contraction-associated proteins, such as OXTR, GJA1 and PTGS2. By contrast, increased expression of genes that ultimately lead to parturition is mediated by enhanced inflammatory and estradiol-17β (E2) and estrogen receptor α signalling, which reduce PR function, thus further intensifying the inflammatory response. To obtain a more complete understanding of the molecular events that underlie the transition of the pregnant myometrium from a refractory to a contractile state, the roles of microRNAs, their targets, and their transcriptional and hormonal regulation have been investigated. This article reviews the actions of the miR-200 family and their P4-regulated targets-the transcription factors ZEB1, ZEB2 and STAT5B-in the pregnant myometrium, as well as the role of miR-199a-3p and miR-214 and their mutual target PTGS2. The central role of ZEB1 as the mediator of the opposing actions of P4 and E2 on myometrial contractility will be highlighted.

Az előzőhöz hasonló végkövetkeztetésre jut: aZEB1 centráli mediátora a P! és az E2 méhizom kontraktilitásra gyakorolt ellentétes hatásának.

J Biol Chem. 2015 Sep 11;290(37):22409-22.

The miR-200 family and its targets regulate type II cell differentiation in human fetal lung.

Benlhabib H et al.

Abstract
Type II cell differentiation and expression of the major surfactant protein, SP-A, in mid-gestation human fetal lung (HFL) are induced by cAMP and inhibited by TGF-β. cAMP induction of SP-A promoter activity is mediated by increased phosphorylation and DNA binding of thyroid transcription factor-1 (TTF-1/Nkx2.1), a master regulator of lung development. To further define mechanisms for developmental induction of surfactant synthesis in HFL, herein, we investigated the potential roles of microRNAs (miRNAs, miRs). To identify and characterize differentially regulated miRNAs in mid-gestation HFL explants during type II pneumocyte differentiation in culture, we performed miRNA microarray of RNA from epithelial cells isolated from mid-gestation HFL explants before and after culture with or without Bt2cAMP. Interestingly, the miR-200 family was significantly up-regulated during type II cell differentiation; miR-200 induction was inversely correlated with expression of known targets, transcription factors ZEB1/2 and TGF-β2. miR-200 antagonists inhibited TTF-1 and surfactant proteins and up-regulated TGF-β2 and ZEB1 expression in type II cells. Overexpression of ZEB1 in type II cells decreased DNA binding of endogenous TTF-1, blocked cAMP stimulation of surfactant proteins, and inhibited miR-200 expression, whereas cAMP markedly inhibited ZEB1/2 and TGF-β. Importantly, overexpression of ZEB1 or miR-200 antagonists in HFL type II cells also inhibited LPCAT1 and ABCA3, enzymes involved in surfactant phospholipid synthesis and trafficking, and blocked lamellar body biogenesis. Our findings suggest that the miR-200 family and ZEB1, which exist in a double-negative feedback loop regulated by TGF-β, serve important roles in the developmental regulation of type II cell differentiation and function in HFL.

A miR200 család és célpontjai – ZEB 1/2 – reguláló szerepe bizonyított az emberi magzati tüdő alveolusok II típusú sejtjeinek differenciálódásában.

http://www.origo.hu/egeszseg/terhesseg

Kiderült, milyen folyamat indítja be a koraszülést

Illyés András

Igen összetett kölcsönhatások zajlanak két gén, illetve a mikroRNS-ként ismert apró, egyszálú nukleinsav-molekulák között.

A szülés megindulásának idejét egy bonyolult, kétszeres negatív visszacsatoláson alapuló molekuláris szabályozó mechanizmus befolyásolja.

Két olyan génről van szó (ZEB1 és ZEB2), amelyek a progeszteron nevű hormonra érzékenyek. A progeszteron alapvető szerepet tölt be a szülés megindításában, mind az egereknél, mind az embereknél. Fontos különbség azonban, hogy az egerek esetében a hormonszint csökkenése indítja meg a szülést, míg a szülő nőkben elsőként nem a hormonszint változik meg, hanem a hormonreceptorok érzékenysége csökken. Ennek következtében azonban végül ugyanúgy lecsökken a vérben keringő progeszteron szintje, majd megindulnak a méhösszehúzódások.

Két gén és a mikroRNS-ek kölcsönhatásai.

Az egerek méhfalában vett mintákban azt tapasztalták a kutatók, hogy a progeszteronszint csökkenését követően - vagyis a szülés megindulása előtt - csökken a ZEB1 gén aktivitása, vagyis kevesebb fehérje íródik át a génről. Ennek hatására fokozódik a már említett mikro-RNS molekulák egyik típusának, az miR-200 molekuláknak a termelődése. Ez visszahat a ZEB1 és a ZEB2 gének aktivitására, csökkentve az aktivitásukat, aminek következtében még több mikro-RNS kezd termelődni – ez az egyik negatív visszacsatolási kör.

A ZEB1 és a ZEB2 által termelt fehérjékről emellett az is kiderült, hogy képesek elnyomni két olyan gén működését, amelyek a méhösszehúzódások megindításáért felelős fehérjéket termelnek. Ezek közé tartozik az oxitocin nevű hormon receptora és a connexin-43 nevű fehérje. Ha csökken a ZEB1 és a ZEB2 szintje, az emiatt egy másik hatással is jár: megnő az oxitocinreceptort és a connexin-43-at kódoló gének aktivitása, és megindul a szülés. Ez a másik negatív visszacsatolási kör.

Ha a progeszteron csökken: ZEB1 gén aktivitása csökken és a miRNS200 termelés fokozódik. Erre a ZEB1 és ZEB2 aktivitása csökken és még több miRNS termelődik.

● ZEB1 és ZEB2 elnyomja a kontraktilitási fehérjék [oxytocin receptor (Oxtr), connexin 43 (Cx43)] termelését kódoló gének működését,

● ha ZEB1 és ZEB2 csökken, az Oxtr és a Cx43 aktivitás fokozódik,

● ez szüléshez vezet.

A koraszülés-kutatás „szent grálja”

a vizsgált mikro-RNS család nem mutat jelentős különbségeket az egérben és az emberben.

Olyan egerekben, amelyeknél mesterséges úton indították meg a koraszülést, a génkifejeződési mintázatok megegyeztek azzal, amit az előző két esetben tapasztaltak, így feltételezhető, hogy a koraszülés során valóban ezek a folyamatok zajlanak le.

„ … ezek a visszacsatolási körök a fontosak a koraszülésben. A kutatók nem figyeltek erre, mert valami sokkal nyilvánvalóbb dolgot kerestek - nem tűnt valószínűnek, hogy épp itt van a kulcs”.

A jövőben új szereket lehet majd kifejleszteni a koraszülés hatékony megelőzésére: ilyenből jelenleg nem sok van, így egy általánosan alkalmazható gyógyszer kidolgozása akár a koraszülés-kutatás „szent gráljának” is nevezhető.

A”szent grál”: a visszacsatolási körök gyógyszeres befolyásolása.

*

Két közlemény kiemelt figyelmet érdemel:

Nat Commun. 2014 Jun 17;5:4108.

Diminished hERG K+ channel activity facilitates strong human labour contractions but is dysregulated in obese women.

Parkington et al.

Abstract
Human ether-a-go-go-related gene (hERG) potassium channels determine cardiac action potential and contraction duration. Human uterine contractions are underpinned by an action potential that also possesses an initial spike followed by prolonged depolarization. Here we show that hERG channel proteins (α-conducting and β-inhibitory subunits) and hERG currents exist in isolated patch-clamped human myometrial cells. We show that hERG channel activity suppresses contraction amplitude and duration before labour, thereby facilitating quiescence. During established labour, expression of β-inhibitory protein is markedly enhanced, resulting in reduced hERG activity that is associated with an increased duration of uterine action potentials and contractions. Thus, changes in hERG channel activity contribute to electrophysiological mechanisms that produce contractions during labour. We also demonstrate that this system fails in women with elevated BMI, who have enhanced hERG activity as a result of low β-inhibitory protein expression, which likely contributes to the weak contractions and poor labour outcomes observed in many obese women necessitating caesarean delivery.

A hERG kálium csatorna

● fokozott aktivitása: a szülés előtti nyugalom „oka”,

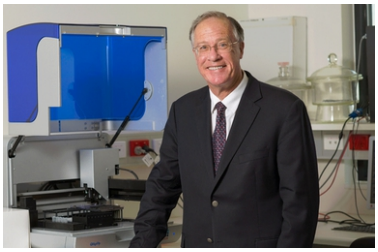
● szülés alatt viszont, a gátló β protein alegység expressziója fokozódik, a hERG aktivitás csökken és erős kontrakciók jelentkeznek.

Elhízott terhesekben azonban ez a folyamat „dysregulált”: a gátló β protein expressziója csökken, a hERG aktivitás fokozódik: gyenge kontrakciók, a szülés elhúzódik, s ezért császármetszés válik szükségessé.

[Az ellenkező irányból megközelítve, elképzelhető, hogy (távlatilag) a myiometrium „korai” aktivitásának gyógyszeres befolyásolásával a koraszülés megelőzhető].

Australian researchers unlock key to triggering labour

the women's
the royal women's hospital
victoria australia



Researcher Prof Shaun Brennecke from the Women's and the University of Melbourne said the finding significantly advances understanding of how labour progresses.

Published today in Nature Communications, this research represents a major advance in our understanding of how labour progresses, with implications for all women who have complicated labours, according to lead researcher Professor Helena Parkington at Monash University's School of Biomedical Sciences.
What she found was that during pregnancy uterine muscle contraction is prevented by electricity flow and this electricity needs to be switched OFF to allow labour contractions to occur effectively. The switch stays turned ON in overweight women. "The reason is stays ON is that the "molecular hand" that should turn the switch OFF fails to appear in sufficient quantities in the uterine muscle of overweight women when labour should be occurring", she says. "These women also respond poorly to our current methods of induction".
This is the first time that the switch and the "molecular hand" controlling it have been identified in uterine muscle.
The clinical significance of this discovery is that, having identified the problem responsible for malfunctioning labour in overweight women, we can now look to developing a safe, effective and specific treatment to correct the problem, for example, a drug that would turn OFF the switch that would allow labour to start and progress.

For more information contact Robyn Riley on (03) 8345 2028

A terhesség folyamán a méh összehúzódásokat kivédi egy bekapcsolt (ON) áramlás (a hERG kálium csatorna), melyet le kell kapcsolni (OFF), hogy hatékony kontrakciók jöhessenek létre,

● túlsúlyos terhesekben viszont ez bekapcsolva (ON) marad: nincs elég „molekuláris lekapcsoló”. Nem is reagálnak fájáskeltőkre.

J Clin Invest. 2015 Jul 1;125(7):2808-24.
Steroid receptor coactivators 1 and 2 mediate fetal-to-maternal signaling that initiates parturition.
Gao L et al.

Abstract
The precise mechanisms that lead to parturition are incompletely defined. Surfactant protein-A (SP-A), which is secreted by fetal lungs into amniotic fluid (AF) near term, likely provides a signal for parturition; however, SP-A-deficient mice have only a relatively modest delay (~12 hours) in parturition, suggesting additional factors. Here, we evaluated the contribution of steroid receptor coactivators 1 and 2 (SRC-1 and SRC-2), which upregulate SP-A transcription, to the parturition process. As mice lacking both SRC-1 and SRC-2 die at birth due to respiratory distress, we crossed double-heterozygous males and females. Parturition was severely delayed (~38 hours) in heterozygous dams harboring SRC-1/-2-deficient embryos. These mothers exhibited decreased myometrial NF-κB activation, PGF2α, and expression of contraction-associated genes; impaired luteolysis; and elevated circulating progesterone. These manifestations also occurred in WT females bearing SRC-1/-2 double-deficient embryos, indicating that a fetal-specific defect delayed labor. SP-A, as well as the enzyme lysophosphatidylcholine acyltransferase-1 (LPCAT1), required for synthesis of surfactant dipalmitoylphosphatidylcholine, and the proinflammatory glycerophospholipid platelet-activating factor (PAF) were markedly reduced in SRC-1/-2-deficient fetal lungs near term. Injection of PAF or SP-A into AF at 17.5 days post coitum enhanced uterine NF-κB activation and contractile gene expression, promoted luteolysis, and rescued delayed parturition in SRC-1/-2-deficient embryo-bearing dams. These findings reveal that fetal lungs produce signals to initiate labor when mature and that SRC-1/-2-dependent production of SP-A and PAF is crucial for this process.

A szteroid receptor koaktivátorok (SRC1, SRC2) közvetítik magzat-anya jelátvitelt, a szülés beindítására.
Ezek „felszabályozzák” az SP-A transzkripciót.

Teljes hiányukban az újszülött egerek

● meghalnak respiratiós distress-ben,

● a kettős heterozigóta anyák szülése megkésett és

●SRC deficiens magzataik tüdejében erősen csökkent az SP-A, a lizofoszfatidilkolin aciltranszferáz 1 (LPCAT1) és a proinflammatórikus thrombocyta aktiváló faktor (PAF).

●SP-A vag PAF intraamniális injekciója kivédte a megkésett szülést.

https://www.facebook.com/anyanaklenni.hu

Kutatók bebizonyították, hogy a magzat indítja el születésének folyamatát a tüdejéből induló molekuláris folyamat révén.

A Texasi Egyetem Délnyugati Egészségügyi Központ (UT Southwestern Medical Center) kutatóinak sikerült azonosítaniuk azt a két fehérjét, amely a szülés megindulásának folyamatához vezet.
A kutatás során **Dr. Carole R. Mendelson** és munkatársai SRC-1 és SRC-2 hiányos egereket tanulmányoztak. A megfigyeléseik szerint a magzatok tüdejében drasztikusan lecsökkent az A felületaktív fehérje (SP-A) és a vérlemezke-aktiváló faktor (PAF) termelődése, ami az állatokban a szülés idejének olyan mértékű eltolódását eredményezte, ami nők esetében a szülés 3-4 hetes késésnek felel meg. Ámha a kutatók A felületaktív fehérjét és vérlemezke-aktiváló faktort injektáltak a fehérjehiányos, terhes állatok magzatvizébe, a szülés időben megindult.
A láncreakció úgy történik, hogy amikor a magzat tüdeje már elég felületaktív anyagot képes kiválasztani ahhoz, hogy az anyaméhből kikerülve önállóan lélegezni tudjon, akkor ez az anyag bekerül a magzatvízbe, ami a méh gyulladását váltja ki: ennek következtében indul be a szülés.

„A tanulmány meggyőző bizonyíték arra vonatkozóan, hogy a magzat szabályozza a szülés beindulását és a szülés időzítése ennek a két gént szabályozó fehérjének (SRC-1 és SRC-2) köszönhető."

„Minél inkább megértjük a normál lefolyású 40 hetes terhesség során a szülés beindításában szerepet játszó tényezőket, annál nagyobb eséllyel tudjuk a koraszülést megakadályozni."

A magyar nyelvű összefoglalás utolsó 4 sora érdemel különös figyelmet.

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