Cervical maturation and labor induction

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Introduction

Cervical maturation is one of the key events in the process of labor, either at term or preterm. The mechanisms involved in cervical ripening start early in pregnancy and increase near parturition. The main changes occur in the cervical connective tissue, mainly the extracellular matrix. They include disorganization of collagen network, increase in hyaluronic acid, increased water content and changes in the proteoglycan content, leading to dramatic changes in the consistency of the cervix.

The pharmacologic control of the cervical ripening process is of major interest, either to allow labor induction in case of an unfavorable cervix, or to prevent preterm delivery in case of premature cervical shortening.

Many substances are known to play a role in the physiologic and pathologic processes of cervical ripening: prostaglandins, relaxin, nitric oxide and inflammatory cytokines may induce cervical priming whereas progesterone play an inhibitory role in the process of cervical ripening and labor induction.

Based on these pathophysiologic data, several compounds and/or interventions have been proposed to induce or conversely to prevent cervical ripening and labor with uneven success. Data from recent studies on cervical maturation and labor induction in case of unripe cervix are presented in this review.

The process of cervical ripening

Changes in the cervical connective tissue start early in pregnancy, probably as soon as the first trimester of pregnancy. A clinically palpable softening of the cervix can be perceived during the 2nd trimester of pregnancy. This softening can be better evidenced by physical measurements of the mechanical properties of the cervix. In humans, Cabrol et al. designed a cervicotonometer, allowing measurements of the distensibility of the human cervix throughout pregnancy. They demonstrated that the changes in the mechanical properties of the cervix start as early as the 1st trimester in humans and continue until term (Figure 1). These changes in the mechanical
properties of the cervix are increasing dramatically in late pregnancy and it is assumed that, in most cases, the cervix is already soft and ripe when the contractions of spontaneous labor begin.

The molecular process underlying the changes in the mechanical properties of the cervix are mainly related to changes in the connective tissue. The sequence of events is very similar to that of inflammation, including release of pro-inflammatory cytokines, infiltration with white blood cells, increase in prostaglandin concentration. This sequence induces activation of degradative enzymes (collagenase, matrix metalloproteinases, MMPs), a decrease in collagen concentration and also changes in the molecules that determine the assembly of collagen fibrils, i.e. glycosaminoglycans (GAG) (Figure 2). Hyaluronic acid concentration increases dramatically during the maturation process. Because of its high molecular weight, it is considered to play a role in the increased tissue hydration. Thus the tight arrangement of the collagen fibrils during pregnancy, gives place to a loose structure with sparse and disorganized collagen fibers. These biochemical changes correlate with the changes in the mechanical properties of the cervix.

**Agents involved in the physiological process of cervical ripening**

Cervical ripening, leading to labor, may occur physiologically at term or in pathological situations before term. Although the process of cervical ripening may seem very similar in these two situations, the initial mechanisms leading to cervical ripening and to labor are thought to be different, at least in some aspects.

**Progesterone** plays a preventive role against the onset
of parturition throughout pregnancy. The mechanisms by which progesterone prevents premature uterine contractions are well described: suppression of genes involved in uterine contractility (gap-junctions, calcium channels, prostaglandin and oxytocin receptors…). The mode of action of progesterone in preventing preterm cervical ripening is less understood but it has been shown that anti-progestin drugs have a cervical ripening effect, as early as the first trimester of pregnancy and throughout pregnancy until term. However, some aspects of cervical ripening occur early in pregnancy, while progesterone concentrations remains at high levels, suggesting that other mechanisms are involved in the ripening process. Furthermore, there is no evidence of a decrease in progesterone plasma concentration in humans near term, suggesting changes in progesterone receptors or in local progesterone concentration.

**Inflammatory cytokines**, and in particular interleukin(IL)-1 and -8, are produced by the cervix and myometrium during pregnancy. The activation of the IL cascade induces neutrophil and macrophage infiltration in the cervix. Both produce MMPs that are involved in the digestion of collagen and other fibrils. Interleukins are produced during the physiological process of cervical ripening and not only during labor induced by inflammation due to ascending bacterial infection. Other cytokines such as TNF-α are mainly produced in response to a bacterial infection. TNF-α induces nitric oxide (NO) synthesis and favors cervical ripening in response to bacterial infection rather than in the physiological conditions.

**Prostaglandins (PGs)**, mainly PGE₂ and PGF₂α, have long been considered key hormones in the mechanism of parturition as they induce both uterine contractions and cervical maturation. Moreover, PG concentration increases during labor in all species, whatever the gestational age. Cyclooxygenase (COX) inhibitors prevent PG production and are powerful tocolytic agents. In a model of rats with remaining cervices after subtotal hysterectomy, PGE₂ induces changes in the GAG distribution, namely increased hyaluronan and water content, some of characteristic patterns of cervical ripening.

Moreover, PGs administered either by systemic or local route, are powerful agents for inducing cervical maturation and labor. However, in physiological situations, the cervical changes occur far before uterine contractions begin and before prostaglandin concentration increase. This strongly suggests that mechanisms other than PGs synthesis are involved in this process of cervical ripening.

**Figure 2. Changes in the cervical connective tissue extracellular matrix from early pregnancy to term.** The tight arrangement of collagen fibers (left) gives place to a loose organization with a decreased collagen density, an increased hyaluronic acid concentration and an increased tissue hydration.
maturation. This is also supported by the fact that COX inhibitors can prevent uterine contractions induced by antiprogestosterone agents but they cannot prevent cervical ripening induced by antiprogestins.  

**NO** has been shown to induce cervical ripening in animals. Cervical ripening in the rat is associated with increased NO production and rats in labor have greater concentrations of NO-synthase, compared with non-laboring rats. After local administration of NO-donor sodium nitroprusside in the cervical canal of guinea pigs, Chwalisz et al. observed an increase in the cervical extensibility and changes in the extracellular matrix similar to those observed in the physiological process of cervical maturation. Conversely, NO-synthase inhibitors such as L-NAME, delay cervical ripening. The involvement of NO as a major actor of cervical ripening would be consistent with the fact that cervical softening occurs during pregnancy, far before uterine contractions. This may also explain why cervical ripening induced by anti-progesterone is not prevented by COX-inhibitors.

**Relaxin** is a peptidic hormone produced by the corpus luteum in rodents and pigs. In these species, relaxin promotes cervical ripening through a positive regulation of MMPs in fibroblasts. In the relaxin gene knockout mice, prolonged labor can be observed, in relation with absent cervical ripening. Contrary to other cervical ripening hormones, relaxin does not induce uterine contractions but has a relaxing effect on the myometrium. It is thus believed to play a role in the conditioning phase of the cervix, far ahead of labor. In humans, relaxin is produced by the decidua. Some studies suggested an increased plasma concentration of relaxin in case of preterm labor but there is to date no indication of an increased synthesis of relaxin before or during labor at term.

### Pharmacological agents used to induce cervical ripening in humans

Based on the factors or hormones involved in the physiological process of cervical ripening, most of these have been tested as cervical ripening agents in human studies.

Exogenous prostaglandins induce cervical ripening in all animal species, regardless of gestational age. Prostaglandins also induce uterine contractions and they have long been considered the final effector agent of labor. The use of natural PGE\(_2\) (dinoprostone) and, to a lesser extent, PGF\(_{2\alpha}\) to induce cervical ripening and labor induction became popular in the 1970’s. Many randomized controlled studies were designed to compare natural PGs to placebo or to oxytocin. Oral, intravenous, extra-amniotic, cervical or vaginal routes were tested but it became rapidly obvious that oral route induced more gastrointestinal side effects and that systemic administration was at risk of cardiopulmonary complications. Thus local administration was then preferred to the others.

To date, there have been more than 63 studies (10,441 women) comparing PGE\(_2\) or PGF\(_{2\alpha}\) to placebo or no treatment. PGE\(_2\) reduced the likelihood of not being delivered after 24 h (RR 0.19 [95%CI: 0.14–0.25]). There was a trend toward decreased cesarean delivery rates (RR 0.89 [0.79–1.00]) and an increase in uterine hyperstimulation with fetal heart rate (FHR) changes (RR 4.14 [1.93–8.90]). The use of sustained-release PGE\(_2\) tablets was associated with a decrease in instrumental delivery rates, compared with vaginal PGE\(_2\) gel (RR 0.51 [0.35–0.76]).

In the case of an unfavorable cervix, the use of oxytocin compared with vaginal PGE\(_2\) (15 studies; 1,041 women), bears a higher risk of not being delivered after 24 h (RR 3.33 [1.61–6.89]); a non-significantly increased risk of cesarean delivery (RR 1.24 [0.93–1.65]); and no difference in uterine hyperstimulation with or without FHR changes.

The synthetic PGE\(_1\) analogue misoprostol has been widely studied and compared with placebo and vaginal PGE\(_2\). For doses >25 mcg, misoprostol was more effective than vaginal PGE\(_2\) in achieving delivery within 24 h but with more uterine hyperstimulations and FHR anomalies. For doses ≤ 25 mcg, misoprostol was comparable to vaginal PGE\(_2\) in terms of efficacy and maternal/fetal side effects.

Recently, a 200 mcg misoprostol vaginal insert was compared to a 10 mg dinoprostone (natural PGE\(_2\)) vaginal insert in a randomized prospective study. The time to vaginal delivery was shorter in the misoprostol group (21.5 h compared with 32.8 h; \(P<0.001\)). The difference was more important in nulliparae (29.2 h compared with 43.1 h; \(P<0.001\); i.e. almost 14 h less with misoprostol). Time to any delivery was also shorter with misoprostol (18.3 h vs 27.3 h; \(P<0.01\)), as well as the time to onset of labor (12.1 h vs 18.6 h; \(P<0.01\)). The cesarean delivery rate was not different between misoprostol and dinoprostone groups (26.0% and 27.1%, respectively). Tachysystole associated with FHR changes was more frequent with misoprostol (10.3 vs 2.8%; \(P<0.001\)). Neonatal outcomes were similar between groups. This new presentation of misoprostol seems to allow shorter time to delivery intervals without increased cesarean delivery rates. The higher tachysystole rate is the counterpart of this higher rapidity of labor and requires close monitoring. The choice between dinoprostone and misoprostol vaginal inserts could be based on parity,
on cervical assessment before labor induction and on the fetal status. Fetuses at higher risk for fetal asphyxia (preterm, small for gestational age, postdates...) would be preferably induced with PGE₂, whereas those without fetal risk factors but with low Bishop score in nulliparae, and in situations where a more expeditious delivery is required, could benefit from induction with misoprostol vaginal insert.

Relaxin was first used as a ripening agent in humans during the 1980’s. The main theoretical advantage of relaxin over other ripening agents is the lack of uterotonic effect and thus the lesser risk of uterine hyperstimulation and fetal hypoxia during labor induction. Moreover, high circulating levels of relaxin have been seen in women delivering preterm, suggesting a potential role of relaxin in the process of labor in women. Although a few reports seemed favorable, neither local (cervical or vaginal) nor systemic use of relaxin induced a significant improvement of labor induction in case of an unfavorable cervix. At the present time, there is no registered drug based on relaxin for cervical ripening or labor induction.

The anti-progestrone drug mifepristone was used in humans in the late 1980’s. It has been shown that anti-progestin drugs have a cervical ripening effect, as early as the first trimester of pregnancy and this effect has been used for cervical preparation before surgical dilation in case of termination of early pregnancy. Mifepristone has also been used for cervical ripening and labor induction at term. Frydman et al. compared mifepristone 200 mg daily to placebo in a randomized controlled trial. They observed a 54% rate of women delivered after 72 h, compared to 19% in the placebo group. There was no difference in the overall cesarean delivery rate between groups. One of the main potential advantages of mifepristone over prostaglandins is, again, the fact that it induces very little increase in uterine contraction pattern. This allows a longer time of cervical maturation without significantly altering maternal tolerance or fetal wellbeing. On the other hand, mifepristone acts slowly and the 54% rate of women delivered after 3 days seems modest, compared to that obtained with prostaglandins. The indication of cervical ripening or labor induction is not mentioned in the labeling of mifepristone either in European or in American drug agencies.

NO-donors have been assessed in humans in several randomized prospective studies. Nineteen studies on sodium nitroprusside or glyceryl trinitrate, for cervical ripening and labor induction were reviewed and 10 were included in a metaanalysis. Although the number of cases treated is relatively limited, there is to date no evidence of a benefit from NO-donors over placebo. On the other hand, maternal side effects like headaches are more frequent with NO-donors.

Obviously, the fact that NO-donors have a relaxing effect on the myometrium make it difficult to imagine very short induction-to-delivery times with this product. One of the best indications would be situations like prolonged pregnancy, were cervical ripening/labor induction is necessary, but with limited urgency. A prospective multicenter randomized study was recently performed in France, comparing ambulatory vaginal isosorbide mononitrate with placebo for cervical ripening and labor induction, in women with prolonged pregnancy after 41 weeks. Again, this study failed to demonstrate any beneficial effect of NO-donors on cervical ripening or labor induction or cesarean delivery rates.

Mechanical methods for cervical ripening have been used for a long time, including amniotomy, sweeping of the membranes, laminaria tents and use of balloon catheters, namely Foley or Cook catheters. Most of these methods are thought to act via the stimulation of endogenous prostaglandin production. Rupture or sweeping or the membranes require a sufficiently opened cervix to introduce a finger or an instrument for amniotomy. Compared with labor induction by oxytocin, the balloon catheter reduced the risk of cesarean delivery (RR 0.57 [0.38–0.88]), without difference in neonatal outcome.

Compared with prostaglandins, labor induction with balloon catheter induced less uterine hyperstimulations with FHR changes (RR 0.19 [0.08–0.43]), but required more frequently oxytocin augmentation (RR 1.51 [1.15–1.97]). The rates of women not delivered within 24 h, the rates of cesarean deliveries and the neonatal outcomes were not different.

Conclusion

Despite constant progress, the physiological mechanisms involved in cervical ripening and onset of labor are still incompletely understood. They provide new prospects in the pharmacological control of parturition and in improving the methods of labor induction.

Although the mechanisms involved in the control of cervical ripening and uterine contraction are different, the most effective compounds for labor induction to date are prostaglandins, which induce both cervical maturation and uterine contractions, with the known possibility of uterine hyperstimulation.

More research is still needed to discover the ideal cervical ripening agent that would act rapidly, without inducing uterine contractions and without risk of altering fetal wellbeing.

Conflict of interest

Bruno Carbonne acts as a consultant for Ferring.
Cervical ripening

Pharmaceuticals.

References