Review Article

Cervical Ripening and Labor Induction: A Current Review

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Abstract

Labor induction is often necessary because of maternal or fetal indications. When performed with an unripe cervix, it results in prolonged labor, potential medical complications, and an increased rate of cesarean section. The purpose of cervical ripening and induction of labor is to achieve vaginal delivery and avoid operative delivery by cesarean section. In this review, we present cellular and biochemical events in cervical ripening and discuss the indications and contraindications of labor induction, and then describe various pharmacologic and mechanical methods for ripening the cervix and inducing labor.

Key words: cervical ripening, induction of labor, pitocin, prostaglandins, mechanical dilators, hygroscopic dilation.

Introduction

Induction of labor is frequently necessary for a variety of maternal and fetal indications. It is well established that cervical status prior to induction of labor has tremendous impact on the success and outcome of the induction process. The overall rate of induction in the United States in 1993 was 134 per 1,000 live births, or more than 527,000 of the 4 million births that occur annually.[1] For induction to succeed, it is extremely important that cervical ripening precedes labor induction.

In this review, we will discuss the cellular and biochemical events in cervical ripening and then describe the various methods for ripening the cervix and inducing labor.

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Cellular and Biochemical Events in Cervical Ripening

Ripening of the cervix is complex, and our understanding of the physiologic mechanisms involved in cervical ripening is far from complete. Cellular aspects of cervical maturation include presence of smooth muscle, collagen, and ground substance or connective tissue. Changes that take place in collagen and in the connective tissue matrix appear to be the primary factors in cervical ripening. Enzymes, hormones, and collagen breakdown by-products control these changes. While various hormones have been implicated in physiology of cervical ripening, prostaglandins appear to play an important role.

Danforth et al were the first to recognize that changes in the structure and biochemistry of connective tissue are key elements of cervical ripening.[2] They demonstrated that during cervical ripening the ground substance becomes more prominent, and the

collagen fibrils previously arranged in an orderly fashion break up. The collagen is embedded in a ground substance consisting of large molecular weight proteoglycan complexes containing a variety of substances called glycosaminoglycans. Chemically, glycosaminoglycans are long, negatively charged disaccharides that contain one hexosamine (glucosamine or galactosamine) and one uronic acid (glucuronic or iduronic). The structure of collagen is a helix of three collagen α chains of approximately 100,000 MW each. Several types of glycosaminoglycans are described, such as heparin, heparan sulfate, dermatan, and chondroitin sulfate. In the cervix, collagen fibrils of proteoglycans are attached by their protein core to glycosaminoglycan side chains and maintain the mechanical strength of the cervix.[3,4] Although there is an increase in the total collagen content of cervix at term, the collagen concentration is reduced by 30-50% compared with the nonpregnant cervix.[5-7] Collagenase or metalloproteinese-1 enzymes are responsible for collagen breakdown. Fibroblasts, leukocytes, macrophages, polymorphs, and eosinophils produce these enzymes.[8,9] Additionally, as pregnancy progresses, there are changes in the cervical proteoglycans and glycosaminoglycans. The concentration of hyaluronic acid increases 12-fold at a cervical dilatation of 2-3 cm. Hyaluronic acid binds water, increases the tissue hydration, and decreases cervical rigidity. This occurs simultaneously with a decrease in tissue level of two predominant proteoglycans, i.e. chondroitin and dermatan sulfate. Changes in the process of cervical ripening is the result of biochemical changes, which include a reduction in collagen concentration, an increase in water content, and changes in proteoglycan/glycosaminoglycan composition.[10]

Factors controlling cervical ripening are complex and often not completely understood. It is speculated that inflammatory mediators play a role in cervical ripening, especially in preterm cervical dilatation. It has been shown that fibroblasts produce certain cytokines, i.e. interleukin-8, and can induce cervical ripening in human as well as in animal models.[11-13] Other cytokines, such as interleukin-1b and tumor necrosis factor-α, also have been shown to produce cervical ripening in animal studies.[14-16] It also is speculated that nitrous oxide, which is a known inflammatory mediator, may be involved in the tissue remodeling that occurs during cervical ripening.[17] It is proposed that programmed cell death (apoptosis) may have a significant role in cervical ripening.[18]

Undoubtedly, natural and synthetic prostaglandins play a role in cervical ripening. The main prostaglandins produced by the cervix are PGE2, PGI2, and, to a lesser extent, PGF2.19 Recently, a prostaglandin E1 analogue, misoprostol, has received increased attention as a highly effective cervical ripening agent.[20,21] Prostaglandin E2-mediated cervical ripening may be due to the breakdown of collagen tissue, alteration in glycosaminoglycans/proteoglycan content, or increased hyaluronic acid concentration, and cervical hydration.[22-26]

Clinically, estrogens such as estradiol have been used to produce cervical ripening.[27-29]

The ripening effects of estrogen on the cervix may be related to the induction of prostaglandin synthesis by estradiol that results in an influx of protease-producing leukocytes, which may be responsible for promoting cervical ripening. Unlike estrogen, progesterone appears to inhibit collagenase activity and also acts as a potent anti-inflammatory agent.[30,31] Human and animal studies support the observation that antiprogesterone agents promote cervical ripening, induce neutrophil influx in cervical tissue, and stimulate prostaglandin synthesis.[32-35] Based on original animal observations, it was postulated that relaxin, a 6-KD dimeric peptide hormone, plays a role in cervical maturation.[36] It has been suggested that relaxin increases collagenase activity in humans via a mitotic effect on fibroblasts.[37] While the specific role of relaxin in human pregnancy is not clearly understood, there is evidence to support its role in cervical maturation and ripening.

Requirements for Induction

Ripening and induction of labor are indicated for a variety of maternal or fetal conditions when benefits either to the mother or to the fetus outweigh the benefits of continuing the pregnancy. The state of the cervix prior to induction of labor has tremendous impact on the outcome of the induction. The goal of induction of labor is to eliminate the potential risks to the fetus with prolonged intrauterine existence while minimizing the likelihood of an operative delivery. Induction of labor is the initiation of uterine contractions before the spontaneous

onset of labor. Induction is done by medical or surgical means to achieve delivery. Maternal and fetal risk benefit analysis should be assessed prior to induction of labor. Before inducing labor, the physician should assure there is an indication for induction, explain the induction procedure, and obtain an informed consent from the patient. A pediatrician should be notified so he can make specific plans for the management of the neonate. Maternal pelvic bony structures should be assessed for their adequacy for vaginal delivery. Fetal weight and presentation should be determined. Most inductions are done at term, when fetal lung maturity is documented. However, the benefit of a premature delivery of a fetus from a hostile intrauterine environment may outweigh the potential risks associated with prematurity. Assessment of fetal lung maturity is often necessary prior to induction of labor. According to the American College of Obstetricians and Gynecologists, if one of the following criteria is met, fetal maturity may be assumed and amniocentesis need not be performed:[38]

- Fetal heart tones have been documented for 20 weeks by nonelectronic fetoscope or for 30 weeks by Doppler.
- It has been 36 weeks since a positive serum or urine human chorionic gonadotropin pregnancy test was performed by a reliable method.
- An ultrasound measurement of the crown-rump length, obtained at 6-11 weeks, supports a gestational age of 39 weeks or more.
- An ultrasound scan obtained at 12-20 weeks, confirms the gestational age of 39 weeks or more determined by clinical history and physical examination.

Cervical status is clearly related to the outcome and success of induction. Historically, uterine cervical assessment has progressed from a qualitative definition (soft, ripe, etc.) to a quantitative, numerically based system. In 1964, Bishop developed a standardized, easily determined scoring system based on dilatation, effacement, consistency, position of the cervix, and station of the vertex (Table 1).[39] Bishop found that when the total cervical score was 8 or more, labor was successfully induced, and the likelihood of vaginal delivery was similar to that observed following spontaneous labor.

A ripe or favorable cervix is considered when the cervix is soft in consistency, 50% effaced, dilated 2 cm or more, anterior in position, and in a vertex engagement in the pelvis. In contrast, a poor cervical score (<4) has been associated with failed induction, prolonged labor, high cesarean section rate, and increased maternal and fetal morbidity. Although the Bishop scoring system[39] has been criticized for the equal value assigned to its various five elements, to date, this method remains the best, easiest to determine, and most predictable in regard to labor outcomes. Initially, Bishop's scoring system was used for multiparous women. It has been extended to nulliparous women with an equal degree of reliability.

Indications and Contraindications of Induction of Labor

Prior to labor induction, a maternal and fetal risk benefit analysis should be performed so the mother and her family understand the indications for induction. Indications for inducing labor include, but are not limited to, the following maternal and fetal conditions: [38,40]

- Hypertensive disorders of pregnancy (preeclampsia, eclampsia, chronic hypertension)
- Diabetes, renal disease, chronic pulmonary disease
- Premature rupture of membranes/chorioamnionitis
- Fetal growth restriction
- Postdate pregnancy
- Logistic factors (e.g., risk of rapid labor, distance from hospital, psychosocial indications)
- Abruptio placentae
- Suspected fetal distress
- Rh isoimmunization
- Fetal demise

Conditions that are contraindications for spontaneous labor are also contraindications for induction of labor. These include, but are not limited to, the following:

- Placenta previa
- Vasa previa
- Previous classical cesarean section, or incision due to metroplasty involving the opening of the uterine cavity
- Cephalopelvic disproportion
- Malpresentation

Table 1. Bishop Scoring System.[39]

	Score			
	0	1	2	3
Dilatation (cm)	Closed	1-2	3-4	5 or more
Effacement (%)	0-30	40-50	60-70	80 or more
Station	-3	-2	-1	+1, +2
Consistency	Firm	Medium	Soft	
Position of cervix	Posterior	Mid position	Anterior	

- Active genital herpes infection
- Invasive cervical carcinoma

The following conditions generally do not constitute contraindications to induction of labor but require special caution:

- Multiple pregnancy
- Grand multiparity
- Polyhydramnios
- Abnormal fetal heart rate not requiring emergency cesarean section
- Maternal heart disease
- Severe hypertension
- Fetal presenting part above the pelvic inlet

Ripening of the cervix and a trial of labor in women with one or more previous low transverse cesarean sections are not contraindicated. In such patients ripening of the cervix and trial of labor with prostaglandin E2 vaginal or intracervical gel, amniotomy, and/or oxytocin infusion are not associated with scar dehiscence, rupture of the uterus, perinatal or maternal morbidity, and mortality when administered in a standard dosing regimen.[38, 41-49]

Methods of Cervical Ripening and Labor Induction

Various methods and agents for cervical ripening and labor induction have been described in obstetrics literature. Table 2 summarizes such methods.

Nipple stimulation is an effective means of cervical ripening and may hasten the onset of labor through endogenous release of pituitary oxytocin.[50]

The mechanism of action of herbal preparations, homeopathic solutions, castor oil, enemas, and acupuncture on cervical ripening and uterine activity is not clear. Mechanical stimulation or irritation of the cervix by balloon catheters, laminaria, or synthetic osmotic dilators (Dilapan, Lamicel) has been shown to trigger release or synthesis of endogenous prostaglandins or extract water from cervical tissue and cause the cervix to expand.[51,52]

The most common methods for cervical ripening and induction of labor are surgical —stripping of the membranes and amniotomy — as well as medical approaches that include the use of oxytocin and prostaglandin preparations.

A. Stripping of the Membranes

Digital stripping of the membranes from the lower uterine segment has been used extensively as a clinical method for induction of labor. This method appears to release prostaglandins from the membranes and adjacent decidua and causes a rise in plasma concentrations of prostaglandins, which provides a possible explanation for initiation of uterine activity following such intervention.[53] Membrane stripping is done digitally once daily for up to three days or once a week during pelvic examinations. Risks associated with this technique include infection, bleeding from a previously undiagnosed placenta previa or low-lying placenta, and accidental rupture of the membranes.

One study indicated that membrane stripping may be associated with decreased incidence of postdate pregnancies.[54] Other prospective randomized control trials show that weekly membrane stripping in an unfavorable cervix was associated with earlier delivery and labor – within 48 hours – as compared with the control group.[55-57] Furthermore, more recent randomized controlled trials were conducted in a relatively small number of patients at term and concluded that membrane stripping reduced the

Table 2. Methods of cervical ripening and labor induction.[49]

- Nipple stimulation
- Herbs: blue/black cohosh, evening primrose oil, red raspberry leaves
- Homeopathic solutions: caulophyllum, cimicifuga, pulsatilla
- Castor oil
- Enemas
- Acupuncture
- Sweeping or stripping of the membranes
- Mechanical dilatation:
  - balloon catheters
  - laminaria japonica
  - synthetic osmotic dilators
- Amniotomy
- Pharmacologic hormonal preparations:
  - prostaglandin E2 (Cervidil, Prepidil, hospital-compounded gels)
  - oxytocin
  - misoprostol (prostaglandin E1 analogue [Cytotec])
  - Mifepristone (RU-486)
  - Relaxin

duration of pregnancy and the need of labor induction. Despite the above studies, further larger randomized trials are needed to confirm efficacy and safety of membrane stripping before it is used routinely for induction.

B. Amniotomy

Artificial rupture of the fetal membranes, or amniotomy, is a commonly employed method of labor induction, especially when used in conjunction with oxytocin infusion. Routine amniotomy is reported to result in modest reduction in duration of labor.[57] However, when it is used in combination with oxytocin infusion, it significantly shortens the interval from induction to delivery.[58] In women with a ripe cervix and a high Bishop score, amniotomy has been reported to be 88% successful in inducing labor.[59] Ideally, amniotomy is performed when the cervix is favorable. In urgent situations when induction of labor needs to be done as soon as possible, i.e. severe preeclampsia, this procedure can be done with minimal cervical dilation if the presenting part is well applied to the cervix. Thus the risk of a cord prolapse can be avoided.

Advantages of Amniotomy

- High success rate
- Observation of amniotic fluid for blood or meconium
- Easy access to insert an intrauterine pressure catheter, apply a fetal scalp electrode, and/or to perform fetal scalp blood sampling if needed

Risks of Amniotomy

- Umbilical cord prolapse/cord compression
- Maternal and fetal/neonatal infection
- Fetal heart rate decelerations
- Bleeding from vasa previa
- Fetal injury

C. Medical Induction of Labor

1. Oxytocin

Oxytocin is the most commonly used drug for induction of labor. There is no physiologic difference between oxytocin-stimulated labor and natural labor. During the first stage of spontaneous labor, oxytocin is released in spurts from the posterior pituitary gland. Its secretion increases during the second stage of labor. The mean plasma half-life of oxytocin is 3-4 minutes, with a range of 2-7 minutes. With intravenous oxytocin infusion, the plasma oxytocin level increases during the first 20 minutes, and a steady plasma concentration is reached in 40 minutes. The plasma level significantly declines when intravenous infusion is discontinued. Oxytocin circulates unbound and is excreted by the liver and kid-

neys. Furthermore, oxytocinase, a circulating enzyme produced by the placenta, degrades oxytocin. The amount of oxytocin being metabolized by placental oxytocinase is equal to the amount infused. During gestation, the oxytocinase activity increases simultaneously with increases in metabolic clearance of oxytocin.[60,61] Myometrial responses to oxytocin levels vary according to status of the cervix, uterine sensitivity, variability in oxytocin clearance rate, duration of pregnancy and preexisting uterine contractions.[62] Myometrial responsiveness to oxytocin begins at 20 weeks of gestation and increases thereafter throughout the pregnancy with its peak response before initiation of labor. The peak coincides with a time when oxytocin receptors are at maximum levels. It appears that oxytocin stimulates production and release of arachidonic acid and prostaglandin F2 α by decidua and results in uterine contractions.[63]

Dosage and Administration

Synthetic oxytocin (pitocin) is available in an injectable form for intravenous, intramuscular use and as a nasal spray. The Food and Drug Administration (FDA) has approved only the intravenous solution of oxytocin for induction of labor. Pitocin infusion can be pulsatile or continuous. Pulsatile infusion has been used for induction of labor as it closely simulates the pulsatile release of the hormone from the posterior pituitary gland during spontaneous labor. It is given every 8 minutes beginning at a dose of 1 mu and doubling the dose every 24 minutes until a uterine contraction is obtained.[64-66] It is believed that oxytocin binds to myometrial receptors, leaving them temporarily unavailable for binding additional, continuously infused oxytocin. This method is more physiologic, requires less oxytocin than continuous infusion, and is beneficial in patients in whom a lower fluid volume is desired. However, the equipment necessary to provide pulsatile oxytocin infusion is not readily available to most practicing physicians, and this technique remains largely investigational.[64-67]

Continuous intravenous infusion is the most widely used method. The solution used usually contains 10 usp units (1 ml) synthetic oxytocin added to 1000 ml of isotonic electrolyte solution.

Significant variation exists regarding the initial dose, interval, and frequency of oxytocin dosage increase. It is shown that following intravenous infusion of oxytocin, uterine response occurs within 3-5 minutes, and a steady plasma concentration is reached in 40 minutes.[68] Some investigators recommend low doses (2-4 mu/min. range), which mimic the normal physiologic pattern of endogenous oxytocin release. Others favor a high (pharmacologic) dose (6 mu/min) of oxytocin for the active management of labor. The maximum dose should not exceed 40 mu/min in any given regimen. Table 3 summarizes various oxytocin dosages and optimal intervals.

Studies have shown that both low dose (physiologic) and high dose (pharmacologic) oxytocin regimens are equally successful in establishing adequate labor.[69-72] It is recommended that an oxytocin dose should be used to produce uterine contractions every 2 to 3 minutes and lasting 60 to 90 seconds with 50 to 60 mmHg intrauterine pressure. Hauth et al showed that most patients achieve normal labor with 3 to 5 uterine contractions with 50 to 100 mmHg per 10 minutes when intrauterine pressure monitoring is used.[74] This corresponds to 150-350 Montevideo units (MVU). Although oxytocin dosage varies, a starting dosage of 0.5-2 mu/min with increases in 1-2 mu/min increments every 30-60 minutes is reasonable.

The following points will assist in achieving a good outcome when administering intravenous oxytocin infusion for induction of labor:

- A clear indication for induction of labor should be established; maternal and fetal status should be evaluated and documented.
- All medical personnel who administer oxytocin should possess a thorough knowledge about physiology, pharmacology, and complications of oxytocin treatment.
- Medical personnel should be able to identify and manage oxytocin complications and/or perform a cesarean delivery when necessary.
- A written protocol for oxytocin administration approved by the medical staff should be available in the labor and delivery unit.
- Prior to infusion, the patient should be informed about potential risks and benefits of oxytocin infusion and an informed consent should be obtained.
- Oxytocin infusion is best controlled by a constant infusion pump.

Table 3. Oxytocin dosages and optimal intervals.[73]

	Examples of Protocols of Oxytocin Infusion for Labor Induction		
Reference	**Initial Dose (mu/min.)**	**Incremental Dose (mu/min.)**	**Preferred Interval Between Doses (min.)**
69	0.5	Doubled	60
70	2.5	2.5	30
71	6	6	20-40
72	1-2	1-2	30

- When the cervix is unripe and the Bishop score is 4 or less, cervical ripening may be achieved by prostaglandin E2 gel or overnight (12-18 hours) low-dose oxytocin.[69] The infusion is started at 0.5 mu/min, doubled hourly to a maximum of 2-4 mu/min, and continued overnight.
- Uterine activity is continually monitored to avoid uterine hyperstimulation. Continuous fetal heart rate monitoring will detect abnormal fetal response to uterine contractions.
- Once labor progresses and the intensity of uterine contractions increases, the oxytocin infusion rate should be reduced or the infusion discontinued to avoid hyperstimulation.
- Initially, uterine activity and fetal heart rate monitoring are done with external devices. Whenever possible, amniotomy, an intrauterine pressure catheter, and a fetal scalp electrode are used to assess uterine contractions, to evaluate fetal heart rate tracing, and to regulate oxytocin infusion rate.
- During active labor, cervical dilatation, effacement, descent of the presenting part and intensity of contractions should be recorded. A graphic documentation using Friedman's labor curve would be most helpful in assessing progress of labor.[75]

Complications of Oxytocin Infusion

a. Uterine Hyperstimulation

Uterine hyperstimulation is defined as uterine contractions more often than every 2 minutes and lasting longer than 90 seconds with or without fetal heart changes. This hyperstimulation refers to either frequent uterine activity or increased myometrial tone, which may result in uteroplacental hypoperfusion and fetal hypoxia. This occurs when the uterine resting tone exceeds 20 mmHg. Excessive uterine contractions may also lead to uterine rupture or abruptio placentae. The mechanism of hyperstimulation may be related to overdosage of oxytocin, increased uterine sensitivity to oxytocin, changes in receptor-binding kinetics or oxytocin-induced prostaglandin production.[76] Uterine hyperstimulation may also be related to increased endogenous oxytocin production by maternal or fetal compartments.[77] Measures necessary for management of uterine hyperstimulation include changing the patient's position to the left side, administration of oxygen and more intravenous fluid, and decreasing or discontinuing oxytocin infusion. If hyperstimulation persists after oxytocin is stopped and a nonreassuring fetal heart rate pattern occurs, intrauterine fetal resuscitation with terbutaline 0.125 mg given intravenously or by subcutaneous injection should be considered for rapid resolution of hyperstimulation.

b. Water Intoxication

Due to its structural and functional similarity to the antidiuretic hormone, oxytocin given in large doses can result in water intoxication that leads to hyponatremia, confusion, convulsion, coma, congestive heart failure, and death. Water intoxication can occur with a large dose of oxytocin (40 mu/min or more) given for prolonged periods. Strict adherence to judicious use of oxytocin and close monitoring of fluid intake and output prevents this serious complication. Whenever patients require a large oxytocin infusion rate, the possibility of abdominal (extrauterine) pregnancy or the presence of placental sulfatase deficiency should be considered.

Placental sulfurylated steroids, which are important in mediating uterine activity, are the main precursors of estrogen produced by the placenta.[78-80]

c. Uterine Rupture

This complication occurs more commonly in multiparous patients with a prior uterine scar, fetal malpresentations and multiple pregnancies, or in patients with an overdistended uterus. Therefore, these conditions are relative contraindications to the use of oxytocin.

d. Other Complications

Abruptio placentae, precipitous delivery, postpartum uterine atony and hemorrhage, and neonatal hyperbilirubinemia are other complications that can occur.[81] Amniotic fluid embolism is a very rare complication of oxytocin infusion. It is more apt to happen when oxytocin is used to induce labor for fetal demise. Hypotension occurs when oxytocin is used intravenously in bolus form.

2. Prostaglandins

The second category of drugs used in medical induction of labor is prostaglandins. A Bishop score of 4 or less denotes an unfavorable cervix and is an indication for cervical ripening. The most commonly used prostaglandins for cervical ripening and induction of labor are prostaglandin E2, which contains dinoprostone as the naturally occurring form of PGE2, and prostaglandin E1, or misoprostol, a synthetic PGE1 analog. Two forms of prostaglandin E2 are available for clinical use: PGE2 gel (Prepidil) and PGE2 vaginal insert (Cervidil). Prostaglandin E2 preparations are used locally intravaginally or intracervically. Several randomized prospective studies have shown that PGE2 is more effective than oxytocin infusion for promoting vaginal birth.[82-5] Histologic changes following local administration of PGE2 in the cervix include a dissolution of collagen bundles and an increase in tissue water content, which leads to cervical softening, effacement, and dilatation.[86] Dinoprostone, when used endocervically, may stimulate the myometrium of the gravid uterus to contract in a manner similar to that of a term uterus during labor. Prostaglandin E2 is extensively metabolized in the lungs, further degraded in the liver and eliminated by the kidneys. PGE2 has a short half-life of 2.5 to 5 minutes. The rate limiting step for inactivation is regulated by the enzyme 15-hydroxy-prostaglandin dehydrogenase (PGDH).[87] The FDA has approved both PGE2 preparations, Prepidil and Cervidil, for cervical ripening in patients at term or near term who have a medical or obstetrical indication for induction of labor. More than 70 prospective clinical trials support the finding that intracervical or intravaginal PGE2 is more effective than a placebo or no treatment in producing cervical ripening and dilatation.[88] It has been reported that in addition to uterine stimulation, PGE2 also increases myometrial sensitivity to oxytocin.[89] Thus PGE2 preparations in small doses shorten the labor-to-delivery interval and decrease the amount of oxytocin required for induction of labor.[90-2] The use of prostaglandins is contraindicated in patients in whom the use of oxytocic drugs is contrainticated (see above). Additional contraindications are allergy/hypersensitivity to prostaglandins in grandmultiparas with six or more deliveries.

A. Prepidil

Prepidil contains 0.5 mg dinoprostone (PGE2) gel packaged in a syringe with a 10-mm and 20-mm catheter. After Prepidil gel administration, the patient should remain in a supine position for at least 15-30 minutes to minimize leakage from the cervical canal. If the desired response is obtained from the initial Prepidil gel, the recommended interval before giving intravenous oxytocin is 6-12 hours. If there is no cervical response, a repeat dose of 0.5 mg dinoprostone should be given 6 hours after the initial dose. The maximum recommended cumulative dose of dinoprostone for 24-hour period is 1.5 mg.[93] Clinical trials have shown that Prepidil effectively improves Bishop scores and increases the chance of initiation of labor during the ripening period.[94]

B. Cervidil

Cervidil is available as a vaginal insert containing 10 mg of dinoprostone.[94] When placed in the posterior fornix of the vagina, it absorbs moisture and swells and releases dinoprostone at a rate of approximately 0.3 mg/hour over 12 hours. Patients should remain in supine position for 2 hours following insertion. Controlled release of PGE2 from the hydrogel provides sufficient quantities of PGE2 to

the cervical receptors to induce cellular changes. The Cervidil insert should be removed by pulling its cord after 12 hours or when active labor begins or uterine hyperstimulation occurs. The Cervidil vaginal insert has an advantage over Prepidil gel in that it can be easily removed should uterine hyperstimulation occur. A safe time interval between PGE2 insertion and oxytocin initiation is not established. Because PGE2 potentiates the effect of oxytocin, Cervidil must be removed before oxytocin infusion is started. Uterine activity and the fetal heart rate should be monitored.

Efficacy and safety of Cervidil have been shown in prospective double-blind controlled trials. Furthermore, it has been demonstrated that use of Cervidil decreases the need for oxytocin.[91,92] Cervidil is well tolerated. In placebo controlled trials, the incidence of maternal adverse effects, i.e. fever, nausea, vomiting, diarrhea, and abdominal pain, were noted in fewer than 1% of patients who received Cervidil. The incidence of uterine hyperstimulation with fetal distress was 2.8%, and hyperstimulation without fetal distress was 4.8%. Fetal distress without uterine hyperstimulation occurred in 3.8% of patients who received Cervidil. In cases of fetal distress when the vaginal insert was removed, there was a return to normal rhythm with no neonatal sequelae.[94] Neonatal adverse outcomes, i.e. low Apgar scores, admission to an intensive care unit, and perinatal morbidity and mortality, are not increased in patients who received PGE2 in comparison to those in whom oxytocin alone was used for induction of labor.

C. Misoprostol

Misoprostol (Cytotec, G.D. Searle, Chicago, Illinois) is a synthetic prostaglandin E1 analogue, available as tablets containing either 100 or 200 mcg of misoprostol. Due to its inhibitory effect on gastric acid secretion, misoprostol is indicated for peptic ulcer prevention in patients taking nonsteroidal antiinflammatory drugs.[96] Because misoprostol has been shown to produce uterine contractions and result in pregnancy termination, the manufacturer does not recommend its use for ulcer treatment during pregnancy. The first report on the use of misoprostol for labor induction in the second and third trimester of pregnancy was published by Neto et al in 1987.[96] Campos et al in 1991 used 50 mcg misoprostol intravaginally during third trimester to induce labor.[97] Their data showed a gestational age-dependent response to misoprostol. The authors reported that 73% of their patients >36 weeks pregnancy delivered within 8 hours compared to 36% of women whose gestational age was ≤ 36 weeks. In 1993, Sanchez-Ramos et al compared 50 mcg intravaginal misoprostol every four hours with either oxytocin or extemporaneously prepared PGE gel plus oxytocin.[98] These investigators demonstrated that patients receiving misoprostol had a significantly shorter induction-to-delivery interval. In 1993, Fletcher et al compared intravaginal misoprostol with a placebo in one series and misoprostol with intravaginal dinoprostone in another series.[99] Misoprostol was found to be more effective than a placebo and equivalent to dinoprostone in efficacy and safety. Buser, Mora, and Arias, in a randomized comparison between misoprostol and dinoprostone for cervical ripening and labor induction, demonstrated that misoprostol was more effective than dinoprostone in producing cervical ripening and shortening the duration of labor.[100] However, in their study, misoprostol caused an increase in cesarean sections associated with uterine hyperstimulation. More recently, Sanchez-Ramos et al in a critical meta-analysis showed that the currently used dinoprostone vaginal insert was less effective than other prostaglandins, including misoprostol, for cervical ripening and labor induction.[101]

Successful induction occurred in 65% of patients treated with misoprostol versus 41.4% of patients receiving dinoprostone, and less oxytocin augmentation was needed in the misoprostol group.[102]

Although the FDA has not approved misoprostol for cervical ripening, it has received increased attention as a highly effective cervical ripening agent. This medication has the advantage of being inexpensive, easy to store, and stable at room temperature, while prostaglandin E2 gel is an unstable compound that must be refrigerated to preserve its potency. The cost of a 100 mcg tablet of misoprostol is estimated at approximately $2, whereas the cost of one Cervidil PGE2 insert is $175.24 at our institution.

Indications and Contraindications:

Investigational protocols recommend the follow-

ing indications and contraindications with the use of misoprostol for cervical ripening.[102-4]

Indications

1. Cephalic presentation
2. Singleton pregnancy
3. Intact membranes
4. Bishop score of ≤4
5. Reassuring fetal heart rate

Contraindications

1. The contraindications of oxytocin use (see above)
2. Estimated fetal weight >4500 gm or other evidence of cephalopelvic disproportion
3. Renal or hepatic dysfunction
4. Suspected chorioamnionitis
5. Previous cesarean delivery
6. History of uterine surgery

Dosage

Two dosage regimens are recommended: A 50-mcg dose is made by cutting a 100-mcg tablet in half and placing one half in the posterior vaginal fornix. This dose can be repeated every 4 hours for a maximum of three doses. The second regimen uses 25 mcg misoprostol every 4 hours (for a maximum of 8 doses). Following the initial misoprostol dosing, subsequent doses can be repeated except when the patient develops uterine contractile abnormalities (tachysystole, hypersystole, hyperstimulation) or nonreassuring fetal heart rate patterns.

- Tachysystole is defined as 6 or more uterine contractions in 10 minutes for 2 consecutive 10-minute periods.
- Hypersystole is defined as a single contraction of at least two minutes in duration.
- Uterine hyperstimulation is defined as tachysystole or hypersystole associated with nonreassuring fetal heart rate pattern.
- A nonreassuring fetal heart rate pattern includes persistent or recurring episodes of severe variable decelerations, late decelerations, or prolonged fetal bradycardia, or a combination of decreased beat-to-beat variability and a decelerative pattern.

It is also recommended that subsequent misoprostol doses should not be given when the cervix is >3 cm dilated and 100% effaced or when spontaneous rupture of the membranes occurs. Following cervical dilatation of >3 cm, uterine contractions should be maintained using oxytocin infusion. The incidence of tachysystole is reduced by 50% when the 25 mcg instead of the 50 mcg misoprostol regimen is used for cervical ripening.

Patients receiving misoprostol should be continuously monitored for uterine activity and fetal heart rate. Adherence to a low-dose misoprostol regimen will probably reduce the incidence of uterine hyperstimulation and subsequent abnormal fetal heart rate pattern and further reduce potential need for cesarean delivery.

Oral Administration of Misoprostol

Recent studies have assessed the oral use of misoprostol for labor induction. In an aggregate of several studies (total 1,191 patients) safety and efficacy of oral versus vaginally administered misoprostol were evaluated. The vaginal misoprostol dose ranged from 25 micrograms every 4 hours to 100 micrograms every 3 hours. The oral dose ranged from 50 micrograms every 4 hours to 200 micrograms every 6 hours. Oral and vaginal misoprostol were equally effective in induction of labor. The incidence of tachysystole, hyperstimulation, low Apgar scores, and rate of admission to neonatal intensive care unit was also similar in both groups.[105-11]

D. Other Methods for Cervical Ripening and Induction of Labor

1. Mifepristone (RU-486)

This steroid, an anti-Progestin agent, is also reported to result in cervical changes and increased uterine activity.[111-4] A French report on RU-486 for induction of term pregnancy showed that 200 mg of RU-486 daily for two days resulted in a higher incidence of spontaneous labor than when patients were not treated with this agent.[115] However, there are not enough studies in the United States to suggest use of mifepristone for cervical ripening and induction of labor.

2. Relaxin

Human relaxin is a polypeptide hormone produced by the corpus luteum, the decidua, and the chorion. It consists of two amino acid chains (A and B chains) linked by two disulfide bonds. These bonds and their positions are identical to insulin. However,

there is no similarity in amino acid sequence and biological properties. Relaxin can cause significant collagen turnover by stimulating collagenases.

Relaxin reduces uterine activity in rats and pigs.[115] It inhibits myometrial light chain kinase and increases the cAMP levels. Relaxin further inhibits the influx of calcium into myometrial cells and promotes membrane hypopolarization. It is unclear whether this inhibitory effect also occurs on human myometrium. Most studies showed no significant effect of relaxin on myometrial strips obtained from pregnant human uteri.[109] It is speculated that the presence of relaxin in the cervix allows cervical ripening.[110] Previous trials using purified porcine relaxin administered vaginally or intracervically in a single application have shown its effectiveness in promoting cervical ripening without maternal or fetal side effects.[116-9] More recently, a randomized, double-blind placebo-controlled trial examined the role of recombinant DNA-produced human relaxin for cervical ripening. This study did not demonstrate any relaxin-related perinatal complication.[110] However, relaxin is not commercially available in the United States as an agent for cervical ripening.

3. *Mechanical Methods for Cervical Ripening*

Mechanical methods (dilators) have been used for many years, mainly for cervical ripening prior to induction of labor with oxytocin. These methods are effective in ripening the cervix and include hygroscopic dilators, osmotic dilators (laminaria japonicum), the 24-French Foley balloon, and the double balloon device (Atad Ripener Device).[120-6] Mechanical stimulation of the cervix may result in endogenous release of prostaglandin or a reflex release of oxytocin. These hormones may play a role in cervical ripening when a mechanical dilator is used. Large studies examining laminaria for preinduction cervical ripening support their use for cervical softening compared with no pretreatment.[127-33] In studies comparing natural and synthetic laminarias and prostaglandin products for the purpose of cervical dilatation for first or second trimester pregnancy termination, Dilapan consistently yielded greater cervical dilation with fewer complications.[122,133,134] It is reported that laminaria ripens the cervix but may be associated with increased peripartum infections.[131,135]

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