Induction of Labor: A Review

KAVITA GOEL*, JAYA K GEDAM†, DISHA A RAJPUT‡, MINAL V BHALERAO*

ABSTRACT

Induction of labor is a common obstetric procedure, and is indicated when the benefits to either mother or fetus outweigh those of continuing the pregnancy. Cervical assessment (Bishop score) at the time of initiation is the best independent predictor of induction success. Although multiple agents are available for labor induction, the most commonly used methods are mechanical methods, prostaglandins and oxytocin. Indication for induction of labor, clinical presentation, safety, cost and patient preference may be used in selecting the method of induction. The goal of labor induction must always be to ensure the best possible outcome for mother and newborn.

Keywords: Labor, induction of labor, oxytocin, prostaglandins

Over the past several decades, obstetricians are fascinated with the process of parturition. Thus, the concerns for maternal well-being and timing of birth have been extensively studied to generate multiple approaches to initiate labor. Some of the methods are still used in current practices. Other methods such as vaginal or uterine douches, stimulant injections thrown into the rectum, and the use of ergot alkaloid have been abandoned because of their “ineffectiveness or poisonous effects on the infant”.1

The incidence of labor induction has continued to rise over the past several decades.2 In developed countries, the number of infants delivered at term following induction of labor can be as high as one in four deliveries.3-5 The World Health Organization (WHO) Global Survey on Maternal and Perinatal Health, conducted in 24 countries which included nearly 3,00,000 observations, showed that 9.6% of them were delivered by labor induction. The survey found that African countries have lower rates of induction of labor (lowest: Niger 1.4%) compared with Asian and Latin American countries (highest: Sri Lanka 35.5%).6

INDUCTION OF LABOR

Induction of labor refers to artificial stimulation of uterine contractions before the true onset of spontaneous labor in order to achieve vaginal delivery by medical or surgical means. Augmentation of labor refers to increasing the frequency and the intensity of already existing uterine contractions in a patient in true labor but progressing inadequately, in order to achieve vaginal delivery.

INDICATIONS AND CONTRAINDICATIONS

For induction of labor, the benefits of early delivery to either mother or fetus should outweigh the risks of pregnancy continuation.7 The indications and contraindications for induction of labor are given in Tables 1 and 2, respectively. Before labor induction, thorough examination of the maternal and fetal condition is necessary (Table 3). Indications and contraindications for induction should be reviewed. Risks and benefits of labor induction should be discussed with the patient and relatives including the risk of cesarean delivery. Confirmation of gestational age is very important and fetal lung maturity status should be performed if indicated (Table 4).7,8 A cervical examination should be performed and documented (Bishop score). Fetal presentation and position should be confirmed. Clinical pelvimetry should be performed and cephalopelvic disproportion (CPD) should be ruled out. According to WHO guidelines, labor induction should be performed at a center, where qualified staff and OT facilities are available for cesarean section. Uterine activity and electronic fetal monitoring (EFM) should be done for all patients undergoing labor induction.

PREDICTION OF LABOR INDUCTION SUCCESS

Bishop’s Score

In 1964, Bishop developed a scoring system to evaluate multiparous women for elective induction at term (Table 5).9,10

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associated with failure of induction in nulliparous women at term with low Bishop score is well-established in the literature.

Cervical Length

Cervical length may predict the success of spontaneous onset of labor post-term. This has been evaluated in numerous studies by sonography. However, results showed sonographic cervical length assessment to perform poorly compared to Bishop score for predicting a successful induction.\(^{11}\)

The higher the Bishop score, the more ‘ripe’ or ‘favorable’ the cervix is for labor induction. Most studies define an unfavorable cervix as a Bishop score of 6 or less. The higher risk of cesarean delivery associated with failure of induction in nulliparous women at term with low Bishop score is well-established in the literature.

### Table 1. Indications for Labor Induction

**Absolute indications**
- Hypertensive disorders: Pre-eclampsia/Eclampsia
- Postdated pregnancy
- Premature rupture of membranes
- Chorioamnionitis
- Intrauterine growth restriction
- Fetal complications: Isoimmunization, oligohydramnios, nonreassuring fetal status
- Maternal medical complications: Diabetes mellitus, renal disease, chronic pulmonary disease
- Intrauterine fetal death

**Relative indications**
- Hypertensive disorders: Chronic hypertension
- Polyhydramnios
- Fetal anomalies requiring specialized neonatal care
- Psychosocial conditions: Previous precipitate labor, distance from hospital
- Previous stillbirth

### Table 2. Contraindications for Labor Induction

**Absolute contraindications**
- Vasa previa or complete placenta previa
- Transverse or oblique fetal lie
- Umbilical cord prolapse
- Prior classical uterine incision or transfundal uterine surgery
- Active genital herpes infection
- Absolute cephalopelvic disproportion, contracted pelvis

**Relative contraindications**
- Malpresentation (breech)
- Cervical carcinoma

### Table 3. Criteria for Induction of Labor

<table>
<thead>
<tr>
<th>Maternal criteria</th>
<th>Fetal criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm indication</td>
<td>Confirm gestational age</td>
</tr>
<tr>
<td>Rule out contraindications</td>
<td>Assess fetal lung maturity status if required</td>
</tr>
<tr>
<td>Perform clinical pelvimetry to rule out cephalopelvic disproportion</td>
<td>Estimate fetal weight (clinically or USG)</td>
</tr>
<tr>
<td>Assess cervical condition (Bishop score)</td>
<td>Confirm fetal presentation and lie</td>
</tr>
<tr>
<td>Discuss risks and benefits with patient and relatives</td>
<td>Confirm fetal well-being</td>
</tr>
</tbody>
</table>

### Table 4. Criteria for Confirmation of Gestational Age and/or Fetal Pulmonary Maturity

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmation of gestational age</td>
<td>Fetal heart tones have been documented as present for ≥30 weeks by Doppler ultrasound.</td>
</tr>
<tr>
<td></td>
<td>≥36 weeks have elapsed since a positive serum or urine human chorionic gonadotropin pregnancy test.</td>
</tr>
<tr>
<td></td>
<td>Ultrasound measurement at &lt;20 weeks of gestation supports gestational age of 39 weeks or greater.</td>
</tr>
<tr>
<td>Fetal pulmonary maturity</td>
<td>If term gestation cannot be confirmed by two or more of the above obstetrical, clinical or laboratory criteria, amniotic fluid analyses can be used to provide evidence of fetal lung maturity. A variety of tests are available. The parameters for evidence of fetal pulmonary maturity are as follows:</td>
</tr>
<tr>
<td></td>
<td>• Lecithin/sphingomyelin (L/S) ratio &gt;2.1</td>
</tr>
<tr>
<td></td>
<td>• Presence of phosphatidylglycerol (PG)</td>
</tr>
<tr>
<td></td>
<td>• TD x FLM assay ≥70 mg surfactant/1 g albumin present</td>
</tr>
<tr>
<td></td>
<td>• Presence of saturated phosphatidylcholine (SPC) ≥500 ng/mL in nondiabetic patients (≥1,000 ng/mL for pregestational diabetic patients)</td>
</tr>
<tr>
<td></td>
<td>• Lamellar body count exceeding 30,000/µL</td>
</tr>
</tbody>
</table>


Table 5. Modified Bishop Score

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Dilation (cm)</td>
<td>Closed</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td></td>
<td>Effacement (%)</td>
<td>0-30</td>
<td>40-50</td>
<td>60-70</td>
</tr>
<tr>
<td></td>
<td>Length (cm)</td>
<td>&gt;4</td>
<td>2-4</td>
<td>1-2</td>
</tr>
<tr>
<td></td>
<td>Station</td>
<td>-3</td>
<td>-2</td>
<td>-1 or 0</td>
</tr>
<tr>
<td></td>
<td>Consistency</td>
<td>Firm</td>
<td>Medium</td>
<td>Soft</td>
</tr>
<tr>
<td></td>
<td>Cervical position</td>
<td>Posterior</td>
<td>Mid-position</td>
<td>Anterior</td>
</tr>
</tbody>
</table>


This modification replaces percent effacement as one of the parameters of the Bishop Score.10

Table 6. Methods of Cervical Ripening

<table>
<thead>
<tr>
<th>Mechanical methods</th>
<th>Surgical methods</th>
<th>Medical methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membrane stripping</td>
<td>Amniotomy</td>
<td>Oxytocin</td>
</tr>
<tr>
<td>Mechanical dilators</td>
<td></td>
<td>Prostaglandins</td>
</tr>
<tr>
<td>Hygroscopic dilators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Laminaria tents</td>
<td></td>
<td>E2 (Dinoprostone)</td>
</tr>
<tr>
<td>* Lamicel</td>
<td></td>
<td>E1 (Misoprostol)</td>
</tr>
<tr>
<td>Foley balloon catheter</td>
<td></td>
<td>Progesterone receptor antagonists (Mifepristone)</td>
</tr>
<tr>
<td>* Without extra amniotic saline infusion</td>
<td></td>
<td>Nitric oxide donors</td>
</tr>
<tr>
<td>* With extraamniotic saline infusion</td>
<td></td>
<td>Estrogen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relaxin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyaluronic acid</td>
</tr>
</tbody>
</table>

Table 7. Standardized Oxytocin Regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Starting dose (mU/min)</th>
<th>Incremental dose (mU/min)</th>
<th>Dosage interval (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose</td>
<td>0.5-2.0</td>
<td>1-2</td>
<td>15-40</td>
</tr>
<tr>
<td>High-dose</td>
<td>6</td>
<td>3-6*</td>
<td>15-40</td>
</tr>
</tbody>
</table>


The incremental increase is reduced to 3 mU/min in the presence of hyperstimulation and reduced to 1 mU/min with recurrent hyperstimulation.

Table 8. Labor Stimulation with Oxytocin: Examples of Low- and High-dose Oxytocin Dosing Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Starting dose (mU/min)</th>
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Fetal Fibronectin

An elevated fetal fibronectin (FFN) concentration in cervicovaginal secretions has been used to predict success of labor induction. An elevated FFN may be caused by disruption or inflammation of the chorionicdecidual interface. A prospective trial concluded that FFN does not predict vaginal delivery in nulliparous women.12 Only obstetric history and digital examination predicted accurately vaginal delivery within 24 hours.13

Cervical Ripening

Cervical ripening is an important predictor of labor outcome. It is a complex chemical change resulting in physical softening and distensibility of the cervix, finally leading to thinning and dilatation of the cervix.14 There is enzymatic dissolution of collagen fibrils of cervix, along with an increase in water content or swelling. These changes are induced by hormones (estrogen, progesterone, relaxin), as well as cytokines, prostaglandins and nitric oxide synthesis enzymes.15 Methods used for cervical ripening include mechanical and pharmacologic methods (Table 6).

Mechanical Methods

Mechanical methods of cervical ripening were among the first methods used for labor induction and have been used for centuries. They are often less costly, result in less hyperstimulation, are easy to store and may result in fewer side effects for mother and fetus are the advantages.16 Risk of infection, disruption of a low-lying placenta and some maternal discomfort on manipulation of the cervix are some disadvantages.

Membrane Stripping

Stripping or sweeping of the fetal membranes is digital separation of the chorioamnionic membrane from the wall of the cervix and lower uterine segment.
This causes the release of endogenous prostaglandins from the adjacent membranes and decidua, as well as from the cervix. Numerous studies have conducted routine membrane stripping at 38 or 39 weeks to either prevent prolonged or post-term pregnancies. Complications include rupture of membranes, hemorrhage from disruption of an occult placenta previa and the development of chorioamnionitis.

**Mechanical Dilators**

Mechanical dilators include hygroscopic dilators (laminaria or lamicel), balloon (Foley catheter) and balloon with extra-amniotic saline infusion (EASI).

**Hygroscopic Dilators**

Cervical dilators are made from organic seaweed (laminaria) or synthetic hydrophilic materials (lamicel-polyvinyl alcohol polymer). They are introduced into the cervical canal and left in situ for 6-12 hours where they increase in diameter because of their hydrophilic properties, achieving a gradual stretching, dilatation and effacement of the cervix.

In the last two decades, there has been a reduction in the use of hygroscopic and osmotic dilators for the induction of labor in favor of the mechanical and pharmacologic agents. Risk of maternal and fetal infections with hygroscopic and osmotic dilators is more as compared with the use of other pharmacologic agents. They are contraindicated in cases of ruptured membranes. Placement of dilators also requires additional training and may be associated with rupture of membranes, vaginal bleeding and patient discomfort or pain.

**Extra-amniotic Balloon and Extra-amniotic Saline Infusion**

The Foley catheter affects cervical ripening in two ways: Gradual dilatation and separation of the decidua from the amnion stimulating prostaglandin release. Foley catheters of size 14-26 F with inflation volume of 30-80 mL, and the EASI with infusion rates of 30-40 mL/hour have been shown to be safe and efficacious. The advantages of Foley catheter when compared with prostaglandins include lower cost, stability at room temperature, reduced risk of uterine tachysystole with or without fetal heart rate (FHR) changes, and applicability in an outpatient setting. It seems that higher insufflations volumes (80 mL) may be more efficacious than lower volumes (30 mL). The concomitant use of oxytocin with Foley catheter does not seem to shorten the duration of labor.

The mean induction to delivery time was shorter with the concomitant use of Foley catheter with vaginal misoprostol. There was no increase in labor complications or adverse perinatal outcomes.

A meta-analysis of randomized controlled trial (RCT) concluded that there was no significant difference between Foley catheter balloon and locally applied prostaglandins in cesarean delivery rates. However, prostaglandins had a significantly increased risk of excessive uterine activity. A RCT concluded that induction of labor using mechanical methods compared to prostaglandins resulted in similar cesarean section rates along with a lower risk of excessive uterine activity. Mechanical methods compared with oxytocin had lower risk of cesarean section. The Foley catheter can be associated with risks of rupture of membranes, vaginal bleeding in women with a low-lying placenta, febrile morbidity and displacement of the presenting part.

**Surgical Method of Induction**

**Amniotomy**

Amniotomy, artificial rupture of membranes, is a procedure carried out by iatrogenic rupture of the chorioamniotic membranes by either toothed clamp (Allis or Kocher’s clamp) or multiple punctures with some pointed structure like 26-guage needle. It is commonly performed in multiparous women with favorable Bishop score with success. However, to minimize the risk of cord prolapse, fetal vertex should not be floating and be well-applied to the cervix. The FHR should be assessed before and after the procedure, and the character and color of the amniotic fluid should be recorded. The concomitant use of amniotomy and intravenous (IV) oxytocin is more effective compared with amniotomy alone, with most women delivering vaginally within 24 hours.

**Pharmacologic Techniques**

**Prostaglandins**

As stated earlier in mechanism of cervical ripening, prostaglandins act on cervix by dissolution of collagen fibrils and an increase in water content of the cervix. Also, prostaglandins increase intracellular calcium levels, causing myometrial contractions. Prostaglandins are already found in the myometrium, decidua and fetal membranes during pregnancy. Initially given by intramuscular and oral routes, nowadays locally applied prostaglandins, vaginally or intracervically, are the routes of choice because of patient acceptability.
with fewer side effects. Side effects include fever, chills, vomiting and diarrhea, etc.

Overall, induction with prostaglandins was associated with an increase in successful vaginal delivery within 24 hours, a reduction in the rate of cesarean delivery and an increase in the risk of uterine tachysystole with FHR changes. Prostaglandins should not be used in women with a prior cesarean delivery or myomectomy because of an increased risk of uterine rupture. Uterine activity and FHR monitoring should be maintained after administration of prostaglandins for cervical ripening.

PGE\textsubscript{2} Dinoprostone

Local application of prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) is commonly used for cervical ripening. Its gel form (Prepidil) is available in a 2.5 mL syringe containing 0.5 mg of dinoprostone. With the woman supine, the tip of pre-filled syringe is placed intracervically to deposit the gel just below the internal cervical os. After administration, she remains supine for at least 30 minutes. Doses may be repeated every 6 hours with a maximum of two doses in 24 hours recommended. A 10 mg dinoprostone vaginal insert (Cervidil) is also approved for cervical ripening. This is a thin, flat, rectangular polymeric wafer held within a small, white mesh polyester sac with long attached tail. It provides slower release of drug (0.3 mg/hr). It is used as a single dose placed transversely in posterior vaginal fornix. Following insertion, a woman should remain supine for at least 2 hours. The insert is removed after 12 hours or with labor onset. These two preparations are costly, and need refrigerated storage to remain stable.

Prostaglandin E\textsubscript{1}

Misoprostol (Cytotec) is a synthetic prostaglandin E\textsubscript{1} (PGE\textsubscript{1}) analog initially used with nonsteroidal anti-inflammatory drugs (NSAIDs) to prevent gastric ulcers and is available as 100 and 200 μg tablets. Misoprostol for preinduction cervical ripening is an ‘off-label’ use. Misoprostol is less costly, safe and is also stable at room temperature. Misoprostol can be administered orally or placed vaginally with few systemic side effects. A Cochrane meta-analysis of trials revealed that vaginal misoprostol improved cervical ripening with an increased rate of vaginal delivery within 24 hours compared with placebo. Compared with PGE\textsubscript{2} also, it gave similar results. However, uterine tachysystole with fetal heart changes was more common. Most studies suggested that restricting the dose of misoprostol to 25 μg every 4 hours significantly reduced the above risk.

In a meta-analysis, oral misoprostol use was found clearly superior to placebo, as women administered 25 and 50 μg oral misoprostol dosages were more likely to deliver vaginally within 24 hours, needed less oxytocin and had a lower cesarean rate.

Some investigators have described titrating oral misoprostol to its desired effect with less uterine overactivity compared to vaginal misoprostol. Low-dose oral misoprostol (20 μg) is achieved by making a solution (e.g., dissolving a 200 μg tablet in 200 mL tap water) and administered every 2 hours.

Other modes of administration include buccal and sublingual route of misoprostol administration. A systematic review concluded that the sublingual route of misoprostol administration is equally efficacious as the vaginal one for labor induction. However, the concerns regarding safety, dosing, side effects and adverse maternal and neonatal outcome need to be studied in future trials for routine recommendation in obstetrics.

Progesterone Receptor Antagonists

RU-486 (Mifepristone) is a more selective progesterone receptor antagonist and has been used for early pregnancy termination. Because of its action, trials had been undergoing for its applicability in cervical ripening and labor induction. The studies suggested that mifepristone reduced the rate of cesarean section as compared to placebo. Therefore, future trials are needed to compare mifepristone with other established cervical ripening agents.

Nitric Oxide Donors

Nitric oxide donors act by increasing the expression of cyclooxygenase-2 (COX-2) in the cervix, thus improving cervical distensibility without causing uterine contractions. Benefits include its use in the outpatient setting, low-cost and ease of administration. Side effects may include maternal hemodynamic changes associated with a vasodilator, including hypotension and tachycardia. Women reported headaches and palpitations as the most common side effects of intravaginal administration of isosorbide mononitrate, 40 mg. A trial comparing isosorbide mononitrate with placebo resulted in no difference in admission to delivery interval despite a clinical effect on cervical ripening. Therefore, further trials are needed for isosorbide mononitrate use as a cervical ripening agent before its acceptance.

Several other approaches to cervical ripening have been documented in literature, including estrogen, relaxin...
and hyaluronic acid, etc. None of them were found to be clinically useful and they have now been superseded by the use of mechanical methods and prostaglandins.

**Medical Methods of Induction**

**Oxytocin**

Oxytocin is a polypeptide neurohormone originating from the hypothalamus and secreted from the posterior lobe of the pituitary gland, representing the agent most frequently used for labor induction. Gestational age is a major factor affecting the dose response to oxytocin with the uterus responding to oxytocin at approximately 20 weeks gestation, with increasing responsiveness with advancing gestational age primarily due to an increase in myometrial oxytocin binding sites. Thereafter, myometrial sensitivity to oxytocin remains more or less same from 34 weeks to term till active labor commences, and the sensitivity increases many fold. Due to this mechanism, oxytocin is better in augmenting labor than in inducing labor, and even less efficacious as a cervical ripening agent.

Oxytocin is mainly given by IV infusion. It is not active orally because it is degraded by gastrointestinal enzymes. The plasma half-life is short, around 3-6 minutes and steady state concentrations are reached within 30-40 minutes of continuous IV infusion. It is prepared by diluting 10 units in 1,000 mL of an isotonic solution. The standardized dosing regimen consists of infusion rate of 2 mU/min or 12 mL/hour with an incremental dose of 2 mU/min or 12 mL/hour every 45 minutes until contraction frequency is adequate (Table 7). Maximum dose is 16 mU/min or 96 mL/hour. IV oxytocin is considered superior to placebo with a significant shorter induction to delivery time. Oxytocin induction may increase the rate of interventions in labor.

**Complications Associated With Induction Of Labor**

**Uterine Overactivity**

This is the most frequently encountered complication of oxytocin or prostaglandin administration. The most commonly used terms to describe are hyperstimulation, tachysystole and hypertonus. The American College of Obstetricians and Gynecologists (ACOG) offers the following definitions:

- **Tachysystole** can be defined as a persistent pattern of ≥ 5 contractions in 10 minutes.
- **Hypertonus** is described as a single contraction lasting longer than 2 minutes.
- **Hyperstimulation** is described as tachysystole or hypertonus associated with FHR abnormalities.

One of the advantages of oxytocin administration is that if uterine hyperstimulation is noticed, the infusion can quickly be stopped. This usually results in the resolution of such uterine overactivity. In addition, placing the woman in the left lateral position, administering oxygen and IV fluids may be of benefit. If FHR tracing abnormalities persist and uterine hyperstimulation is ongoing, the use of a tocolytic such as terbutaline may be considered.

**Failed Induction**

There are currently no criteria for a failed induction. The obstetrician should understand that cervical ripening itself can take some time, and that the establishment of an active labor is important to label labor as failed induction. A study concluded that 40% of the women who remained in the latent phase after 12 hours of oxytocin and membrane rupture were delivered vaginally. Therefore, it is important not to label labor induction a failure in the latent phase until oxytocin has been administered for at least 12 hours after membrane rupture. Failed induction is not necessarily an indication for cesarean section. Other options include a further attempt to induce labor (the timing should depend on the clinical situation and the patient’s wishes) or waiting for spontaneous labor.
Cesarean Section

Increasing incidence of labor induction has contributed to the increasing cesarean section rate. Compared to spontaneous onset of delivery, induction of labor is associated with an increased risk for emergency cesarean section both among nulliparous and multiparous women.44-46

Greater Need for Pain Relief

Induced labor significantly differs from the physiological spontaneous onset labor, with a longer and often painful latent phase. Prostaglandins may be associated with significant discomfort. Simple analgesia may suffice, but some women will require stronger opiate/epidural analgesia.

Uterine Rupture

Uterine rupture is rare and in most instances occurs in women with prior uterine surgery such as cesarean delivery or myomectomy. Other risk factors are grand multiparity, marked uterine overdistension either with a macrosomic fetus, multiple gestation, polyhydramnios, or fetal malpresentation. Most studies suggest that the use of oxytocin for labor induction or augmentation is not associated with a significant increase in the risk of uterine rupture in women with a prior cesarean delivery. The ACOG states that the use of misoprostol in women with prior cesarean delivery or major uterine surgery has been associated with an increase in uterine rupture and, therefore, should be avoided in the third trimester.

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