

Methods of inducing labor

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1 Introduction

For practical purposes, modern obstetric practice uses only three broad approaches to the induction of labor: mechanical methods (such as

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sweeping of the membranes or use of a dilator); amniotomy (artificial rupture of the membranes); and oxytocic drugs (oxytocin or a prostaglandin). Other methods, although still occasionally reported, have generally been abandoned. Traditional practices, such as the use of castor oil, have not been formally evaluated.

Standardized 'scoring' of the cervix prior to labor induction has been recommended, although cervical dilation alone may be more predictive of successful labor induction. Oxytocin has the disadvantages of a high failure rate when the cervix is unfavorable (low cervical score), and it requires monitoring of continuous intravenous infusion. Artificial rupture of membranes is also less effective or may not be possible when the cervix is unfavorable.

Unsuccessful labor induction is most likely when the cervix is unfavorable and, in this circumstance, prostaglandin preparations have proved to be beneficial. Uterine hyperstimulation has been identified as a potential problem during labor induction with prostaglandins; on occasion this has warranted treatment with tocolytics (see Chapter 39).

2 Mechanical methods

2.1 Sweeping (stripping) the membranes

Sweeping the membranes (digital separation of the fetal membranes from the lower uterine segment) has been used for many years to induce labor or to pre-empt formal induction of labor with either oxytocin, prostaglandins, or amniotomy. There are good theoretical reasons to suggest that it may be effective, in that it stimulates intra-uterine prostaglandin synthesis. When the cervix is closed, a cervical massage has been proposed.

Studies have been conducted to evaluate stripping/sweeping of the membranes, either as a general policy in women at or near term to prevent post-term pregnancy or in a selected group of women thought to require labor induction. The available evidence suggests that sweeping of the membranes reduces the duration of pregnancy, and thus the proportion of women requiring formal labor induction for 'post-dates' pregnancy. For women thought to require induction of labor, a reduction in the use of more 'formal' methods of induction could be expected. However, no clear benefits on substantive outcomes (e.g. caesarean section) were reported.

Sweeping of the membranes is probably safe, provided that the intervention is avoided in pregnancies complicated by placenta praevia or

when contra-indications for labor and/or vaginal birth are present. There is no evidence that sweeping the membranes increases the risk of maternal and neonatal infection. A trend towards an increased frequency of prelabor rupture of membranes was noted. Women's discomfort during the procedure, and 'minor' side-effects must be balanced with the expected benefits before submitting women to a sweeping of the membranes.

2.2 Other mechanical methods

Mechanical methods were the first methods developed to ripen the cervix or to induce labor. Devices that were used in this context include various type of catheters and laminaria tents, introduced into the cervical canal or through the cervix into the extra-amniotic space. Mechanical methods were never completely abandoned but during recent decades have been largely replaced by pharmacological methods. Potential advantages of mechanical methods over pharmacological ones may include simplicity of use, lower cost, and reduction of some of the side-effects. The goals of these interventions are to ripen the cervix through direct dilatation of the canal or, indirectly, by increasing prostaglandin and/or oxytocin secretion. In addition, these methods may lead to labor onset. The Foley catheter is currently used, as well as a specially developed 'Atad' double-balloon catheter. The catheter is introduced through the cervical canal to reach the extra-amniotic space. The balloon is then inflated to keep the catheter in place. Traction is sometimes applied to the catheter. In addition, some clinicians inject saline or prostaglandins in the extra-amniotic space, in an attempt to enhance the efficacy of the method.

Laminaria tents, made from sterile sea-weed or synthetic hydrophilic materials (e.g. Lamicel), are introduced into the cervical canal to achieve a gradual stretching of the cervix. In addition to the local effect, mechanisms that involve neuroendocrine reflexes (the Ferguson reflex) may promote the onset of contractions.

3 Amniotomy

3.1 Amniotomy used alone

Amniotomy (rupturing the membranes) can induce labor but its use implies a firm commitment to delivery; once the membranes have been ruptured, there is no turning back. The main disadvantage

of amniotomy, when used alone for the induction of labor, is the unpredictable and, occasionally, long interval to the onset of uterine contractions and thus to delivery. It may increase the risk of infection if labor does not proceed promptly. Rupture of the membranes may also increase the vertical transmission of specific maternal infections, such as HIV.

3.2 Amniotomy with oxytocic drugs versus amniotomy alone

In order to shorten the interval between amniotomy and delivery, oxytocic drugs are usually used either at the time that the membranes are ruptured or after an interval of a few hours if labor has not started. Evidence from controlled trials shows that women who receive oxytocics from the time of amniotomy are more likely to be delivered within 12 and 24 hours, and less likely to give birth by cesarean section or forceps, than those who have had amniotomy alone.

Women who receive early oxytocin use less analgesia than those receiving oxytocin later. This does not necessarily mean that early oxytocin results in a less painful labor for these women; it may simply reflect the shorter interval between amniotomy and birth. The trials for which data are available also suggest a lower incidence of postpartum hemorrhage when amniotomy is combined with early oxytocin administration.

Low Apgar scores are seen less frequently with a policy of using oxytocin from the time of amniotomy. No other differential effects on the baby have been noted in controlled trials.

3.3 Amniotomy with oxytocic drugs versus oxytocic drugs alone

When compared with a policy in which the membranes are left intact, routine amniotomy at the time of starting oxytocic drugs to induce labor is more likely to result in established labor within hours of starting the induction. The limited number of controlled trials precludes firm conclusions on other outcome measures, such as the likelihood of birth within 24 hours, cesarean section, or perinatal morbidity and mortality.

Observational data derived from studies conducted in the 1960s, however, suggest that about a third of women in whom induction of labor is attempted with oxytocin administration but without concurrent amniotomy, will remain undelivered 2–3 days after the beginning of the induction attempt. Not surprisingly, in the light of these observations, amniotomy has come to be used routinely at the time that oxytocin is started to induce labor. Only with the development of

prostaglandin preparations has the choice of leaving the membranes intact during induction of labor become a reasonable option.

3.4 Hazards of amniotomy

A number of undesirable consequences have been attributed to artificial rupture of the membranes. These include: pain and discomfort; intra-uterine infection (occasionally leading to septicemia); early decelerations in the fetal heart rate; umbilical cord prolapse; and bleeding, either from fetal vessels in the membranes, from the cervix, or from the placental site. Serious complications, fortunately, are rare.

Any instrument (or a finger) passing up the vagina in order to rupture the amniotic sac will carry some of the vaginal bacterial flora with it. The risk of clinically significant intra-uterine infection ensuing from these procedures depends largely on the interval between amniotomy and delivery.

The view that amniotomy predisposes to fetal heart-rate decelerations, is largely based on potential cord compression due to diminished amniotic fluid volume, but there is no evidence that this risk is important enough to be a main determinant in choosing a method for the induction of labor.

4 Oxytocin

4.1 Routes and methods of administration

No formal comparisons between the usual intravenous route and other routes of administration have been reported.

Intravenous oxytocin has been administered in different ways ranging from simple, manually adjusted, gravity-fed systems, through mechanically or electronically controlled infusion pumps, to fully automated closed-loop feedback systems in which the dose of oxytocin is regulated by the intensity of uterine contractions. Gravity-fed systems have the disadvantage that the amount of oxytocin infused may be difficult to regulate accurately and may vary with the position of the woman. A further disadvantage is that the amount of fluid administered intravenously may be large, and may thus increase the risk of water intoxication. Automatic oxytocin-infusion equipment, by contrast, delivers oxytocin at a well-regulated rate, in a small volume of fluid. In theory it should optimize efficacy and safety during oxytocin administration, but there is no evidence that these theoretical advantages confer any benefit in practice.

The only formal comparisons of different methods for administering oxytocin to induce labor consist of trials comparing automatic oxytocin-infusion systems with 'standard regimens'. These trials have been too small to detect differences in substantive outcomes. The merits and risks of automated infusion systems and alternative dose regimens must be more thoroughly evaluated before their place, if any, in clinical practice can be determined.

4.2 Hazards of oxytocin administration

The possible hazards of oxytocin *per se* must be distinguished from the hazards associated with any attempt to induce labor, and those associated with any artificial stimulation of uterine contractions.

The antidiuretic effect of oxytocin can result in water retention and hyponatremia, and may lead to coma, convulsions, and even maternal death. These risks are mainly associated with oxytocin infusions at early stages of pregnancy, when uterine sensitivity to oxytocin is far less than it is at term and when much larger doses are required to stimulate uterine contractions. In women with an already reduced urinary output, the danger of water intoxication is an important consideration at any stage of gestation.

Any agent that causes uterine contractions, whether it be a drug such as oxytocin or a prostaglandin, or a practice such as nipple stimulation, may also cause excessive uterine contractility. Excessively frequent or prolonged uterine contractions may affect blood flow from and to the placenta, which will in turn reduce fetal oxygenation. Uterine rupture is a further, though much rarer, consequence of excessive stimulation of uterine activity. The balance of evidence suggests that induction of labor with oxytocin increases the incidence of neonatal hyperbilirubinemia.

5 Prostaglandin E₂

5.1 Comparisons with placebo

Prostaglandins have been evaluated against placebo for the induction of labor. Not surprisingly, the rates of 'failed induction' and the proportions of women needing a second induction attempt are lower with prostaglandin administration (in various doses, formulations and routes) than with placebo treatments. There were fewer cesarean sections in the prostaglandin than in the placebo groups in the reported trials, but the rates of instrumental vaginal delivery rates were similar.

Most of the trials mentioned specifically that 'uterine hypertonus' and/or 'uterine hyperstimulation' were not observed, and several commented on the low incidence of gastro-intestinal side effects encountered.

Very few infant outcomes were reported in any of these trials. Among those in which they were reported, none showed any differences between the prostaglandin and placebo groups.

For prelabor rupture of membranes at or near term, induction of labor by prostaglandins compared with expectant management, decreases the risk of maternal infection (chorio-amnionitis), neonatal antibiotic therapy, and admission to neonatal intensive care, without increasing the rate of cesarean section, although it is associated with a more frequent maternal diarrhea and use of anesthesia and/or analgesia. In the trials that systematically collected information on women's views, women were more likely to view their care positively if labor was induced with prostaglandins as opposed to expectant management.

5.2 Prostaglandin E₂ versus prostaglandin F

Both PGE₂ and PGF_{2 α} (which are also naturally formed during spontaneous labor) have been used for the induction of labor.

In order to achieve a similar effect on uterine contractility, PGF_{2 α} must be administered in a dose eight to ten times as large as that needed when PGE₂ is used. This difference in potency applies to the stimulating properties of these compounds on the myometrium. It does not apply, to the same extent, to their effects on other organ systems, such as the gastro-intestinal tract. Consequently, for a comparable uterotonic effect, the incidence of side-effects tends to be larger with PGF_{2 α} than with PGE₂. Because of this, PGF_{2 α} is no longer used and PGE₂ has become the only natural prostaglandin used for induction of labor.

5.3 Routes and methods of administration

Early studies of prostaglandins for the induction of labor used the intravenous route of administration. These studies showed few, if any, advantages of prostaglandins over other methods. Compared with oxytocin, they offered no real benefit and were considerably more expensive.

Oral administration of PGE₂ (in repeat doses increasing from 0.5 to 2 mg) became widely used as an alternative to intravenous infusions of prostaglandins for inducing labor, particularly when combined with amniotomy and in women with a favorable cervix. Gastro-intestinal side-effects were common and oral administration has been almost

entirely replaced by vaginal administration, especially since the newer formulations using viscous gel became available.

Because intravenous, oral and, to some extent also, the vaginal administrations of prostaglandins, lead to high levels of these drugs in the blood, the gastro-intestinal tract, or both, intra-uterine (extra-amniotic) routes of administration have been used in attempts to reduce the side-effects associated with the other routes. Continuous or intermittent extra-amniotic infusion of a PGE₂ solution and extra-amniotic injection of a PGE₂ gel suspension have been used for this purpose.

There is a limited amount of controlled data comparing the extra-amniotic route with other routes of prostaglandin administration. Although the data are too limited for a precise estimate, they show no advantage for the more invasive extra-amniotic route, which is both cumbersome and inconvenient for the mother.

Another route of local administration, injection of PGE₂ in a viscous gel into the cervical canal, has been used mainly for ripening the cervix rather than for induction. The relative merits and hazards of endocervical versus vaginal administration have been assessed in a few trials. These have not indicated that either one of these approaches is clearly superior to the other, in terms of substantive outcome measures. The more complex and uncomfortable endocervical insertion procedure is, therefore, difficult to justify.

5.4 Hazards of prostaglandin E₂ administration

The specific hazards attributable to prostaglandins *per se* relate mainly to their effects on the gastro-intestinal tract (nausea, vomiting, and diarrhea). These effects are minimal when the drugs are administered vaginally, endocervically, or extra-amniotically, and maximal when routes of administration (intravenous, oral) that lead to high levels of the drugs in either the blood or the gastro-intestinal tract are used.

Fever may result from a direct effect of prostaglandins on thermoregulating centers in the brain. This is particularly a problem with systemic prostaglandin E₂ administration, and may give rise to concern that intra-uterine infection has supervened. This concern may be further fuelled by a rise in the leucocyte count, which can also be stimulated by prostaglandin administration. Fever is rarely observed with the newer vaginal and endocervical preparations.

More worrying than the specific hazards associated with prostaglandins, are concerns that the simplicity of their administration may

encourage their use for trivial indications or without adequate surveillance of mother and fetus.

6 Prostaglandin E₂ versus oxytocin for inducing labor

The important question is whether prostaglandin E₂ is, on balance, superior to oxytocin for the induction of labor, particularly when the cervix is 'unripe'.

6.1 Effects on time and mode of delivery

The total amount of uterine work required to achieve delivery is lower with prostaglandin E₂ than with oxytocin, presumably because the former also influences connective tissue compliance (cervical 'ripening'), whereas the latter does not. The proportions of women who give birth within 12 hours after the start of induction are similar for women induced with prostaglandin E₂ and for those induced with oxytocin. By 24 hours, however, fewer women have not given birth after induction with prostaglandin E₂, and after 48 hours the proportion of women who have not given birth shows an even larger difference in favor of prostaglandins. When only women who give birth vaginally are considered, this advantage of prostaglandin E₂ becomes even more pronounced.

There is no clear evidence of a differential effect of prostaglandin E₂ and oxytocin on the cesarean-section rate. The rate of instrumental vaginal delivery is lower in the women induced with prostaglandins, as is the incidence of operative delivery overall. This may be due partly to prostaglandins' influence on connective tissue and partly to the greater freedom of movement allowed because it is not administered intravenously.

6.2 Effects on the mother

There are some major differences between the effects of oxytocin and prostaglandins on organ systems other than the uterus. More women experience gastro-intestinal side-effects, such as nausea, vomiting, and diarrhea, when prostaglandins rather than oxytocin are used for the induction of labor. Fever during labor is more likely to occur with prostaglandins than with oxytocin, although the differential effect is found only in the earlier studies of intravenous PGE₂.

Uterine hyperstimulation occurs more frequently with prostaglandin than with oxytocin administration. This complication is seen mainly in institutions with little experience in the use of prostaglandin and was not observed in many trials. A diagnosis of hyperstimulation may lead to a variety of interventions ranging from changes in position, through fetal scalp blood sampling, administration of betamimetic agents, and cesarean section. Thus hyperstimulation is important to the mother, irrespective of whether or not it directly jeopardizes her or the fetus.

Data on the incidence of retained placenta, of postpartum hemorrhage, and of fever during the puerperium, show no difference in the effects of prostaglandin E_2 and oxytocin.

Few data on mothers' views of induction have been reported but they are consistently in favor of prostaglandin E_2 administration, which is considered to be more agreeable, more natural, and less invasive than intravenous administration of oxytocin.

6.3 Effects on the infant

In view of the increased incidence of uterine hyperstimulation associated with induction using prostaglandin E_2 , it is reassuring to note that the incidence of fetal heart-rate abnormalities is similar in labors induced with prostaglandin E_2 and among fetuses of women receiving oxytocin.

Unfortunately, few trials provide data on substantive infant outcomes, such as resuscitation of the newborn, admission to a special care nursery, or early neonatal convulsions. Even data on perinatal death are only available from half of the trials. From those trials that provide data, no differential effects of prostaglandin E_2 and oxytocin emerge, but the precision of these estimates is extremely low.

Somewhat more data are available on the incidence of low 1-min and 5-min Apgar scores, but these show no statistically significant differences between prostaglandin E_2 and oxytocin inductions.

The incidence of neonatal hyperbilirubinemia (jaundice) appears to be lower among infants born after induction of labor with prostaglandin E_2 than among those born after induction with oxytocin, but the difference found may have arisen by chance.

6.4 Prelabor rupture of membranes at or near term

Induction of labor with prostaglandin E_2 increases the number of vaginal examinations and the risk of maternal infection (chorioamnionitis).

It may also increase the risk of neonatal infection, but the harmful effect of induction of labor with prostaglandin E_2 on this outcome may be less than suggested by the Cochrane review. In only one trial was the search for, and determination of, neonatal infection conducted blind to the allocation group and duration of membrane rupture. Induction of labor with prostaglandins increases the rate of neonatal antibiotic therapy and admission to neonatal intensive care for more than 24 hours.

There is no evidence from high-quality trials that a policy of induction of labor with prostaglandin E_2 increases or decreases the rate of cesarean section, although it is associated with a less frequent use of epidural analgesia and internal fetal heart-rate monitoring.

7 Misoprostol

The prostaglandin preparations that have been registered for cervical ripening and labor induction are expensive and unstable, requiring refrigerated storage. Misoprostol (Cytotec, Searle) is a methyl ester of prostaglandin E_1 and is marketed for use in the prevention and treatment of peptic ulcer disease caused by prostaglandin-synthesis inhibitors. It is inexpensive, easily stored at room temperature, and has few systemic side-effects. It is rapidly absorbed orally and vaginally. Misoprostol has been used widely for obstetric and gynecological indications, despite the fact that it has not been registered for such use. It has, therefore, not undergone the extensive testing for appropriate dosage and safety required for registration. Third-trimester cervical ripening and labor induction with misoprostol have been reported using the oral, vaginal and rectal routes.

Results from several trials show that vaginal misoprostol (in dosages ranging from 25 micrograms 2–3-hourly, 50 micrograms 4-hourly (most studies), to 100 micrograms 6–12-hourly) appears to be more effective than oxytocin or dinoprostone in the usual recommended doses for induction of labor. It is associated, however, with increased rates of meconium-stained liquor and of uterine hyperstimulation, both with and without fetal heart-rate changes. The rates of cesarean section were inconsistent, tending to be reduced with misoprostol. No differences in perinatal or maternal outcome were shown. However, the trials were not sufficiently large to assess the likelihood of uncommon, serious adverse perinatal and maternal complications. The possibility of inadvertent bias because of the unblinded nature of these studies should be kept in mind.

A lower dosage regimen of misoprostol (25 micrograms 6-hourly) was less effective than a higher dose (25 micrograms 3-hourly), with possibly reduced rates of uterine hyperstimulation.

The finding of a significant increase in meconium-stained liquor with misoprostol is of interest. One study suggested the possibility of meconium passage in response to uterine hyperstimulation or a direct effect of absorbed misoprostol metabolites on the fetal gastro-intestinal tract.

Misoprostol administered orally is also an effective method of inducing labor, and has the advantage of convenience and avoidance of internal examinations. As for vaginal misoprostol, insufficient data have been produced to evaluate the safety of this approach.

Thus, though misoprostol shows promise as a highly effective, inexpensive, and convenient agent for labor induction, it cannot be recommended for routine use at this stage. It is also not registered for such use in many countries.

Because of the enormous economic and possible clinical advantages of misoprostol, there is the need for further trials to establish its safety.

8 Conclusions

The most important decision to be made when considering the induction of labor is whether or not the induction is justified, rather than how it is to be achieved. Whatever method is chosen to implement a decision to induce labor, uterine contractility, and maternal and fetal well-being must be monitored carefully.

Amniotomy alone is often inadequate to induce labor. When amniotomy is used to induce labor and fails to result promptly in adequate uterine contractility, oxytocic drugs should be administered. The administration of oxytocin without amniotomy is also associated with an unacceptable failure rate.

Prostaglandins are more likely than oxytocin to result in vaginal birth within a reasonable length of time after the start of induction, and to lower the rate of operative delivery associated with induction of labor. The extent to which this may reflect the greater mobility possible with some forms of prostaglandin administration, than with intravenously administered oxytocin, is unknown. These positive effects of prostaglandins must be balanced against their negative effects, troublesome gastro-intestinal symptoms or fever, although these are rarely seen with the newer formulations of prostaglandin E₂ that are now available.

If a decision has been made to use prostaglandins to induce labor, the best option appears to be vaginal administration of prostaglandin E₂ in a viscous gel. PGF_{2α} should no longer be used.

There is too little evidence to allow any judgement about whether prostaglandins are more or less safe for the baby than oxytocin.

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