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Pharmacological aspect of induction of labour and cervical ripening

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Abstract
There has been a growing trend in the number of women who require induction of labour (IOL) and cervical ripening. IOL should be performed only in cases where there is a clear medical indication and the expected benefits outweigh the potential harms. Cervical ripening methods include both mechanical (e.g., intracervical balloon catheter; membrane sweeping and Laminaria etc.) and pharmacological methods (e.g., prostaglandins and oxytocin). IOL is associated with potential risks to both the woman and her foetus. This article provides a review of the trends of induction of labour and cervical ripening, medical indications, different methods of indication and associated risks of IOL.

Keywords: Cervical ripening, foley catheter, induction of labour, oxytocin, prostaglandin

Introduction

Introduction and Epidemiology

Induction of labour (IOL) refers to the process of artificially stimulating the uterus in order to start labour. Globally, there are more than 130 million births [1] with approximately 10% of them undergoing a labour induction during pregnancy [1]. This equates to more than 13 million [1] women undergoing an induction each year with this number continuing to increase. The rate varies greatly among countries depending on income status, resource availability, the presence and adherence to guidelines regarding methods of induction and indications for induction. In high-income countries such as the United States and United Kingdom, the prevalence of labour induction is about 20%[1,2], while in low-income countries of Africa, it ranges from 1.4% to 6.8% [1]. Asian and Latin-American countries have a similar overall prevalence between 12.1% and 11.4% respectively [1]. These great differences in the prevalence of induction of labour among regions could be related to challenges in drug availability, obstetric and foetal monitoring facilities and healthcare staffing in low as compared to high-resource settings. Other important contributors to differences are the lack of adherence to guidelines and protocols in some regions like Africa where 66% to 80.2% of inductions [1] are unindicated and a great variety of practices regarding elective induction of labour. As the number of women who require labour induction increases, the number of women who will have poor Bishop-scores and will require cervical ripening, also rises [3].

Clinical Indications for IOL

The World Health Organization (WHO) envisions a world where "every pregnant woman and newborn receives quality care throughout the pregnancy, childbirth and the postnatal period". According to WHO, induction should be performed with a clear medical indication and when expected benefits outweigh potential harms [1, 2]. It is not surprising that as IOL intervenes in the natural process of pregnancy and labour, it is associated with higher rates of certain complications such as bleeding, caesarean deliveries, uterine hyperstimulation, or rupture and adverse perinatal outcomes [1]. Various clinical factors should be taken into account when considering an induction for a woman. These factors include, but are not limited to, maternal medical conditions (e.g., hypertension and pregestational diabetes), foetal conditions (foetal growth restriction, oligohydramnios and multiple gestation), gestational age (and how the pregnancy is dated) as well as cervical exam and hospital/birth centre resources [4].

Post term Pregnancies: IOL is universally recommended in order to avoid a prolonged pregnancy. Delivery after 42 weeks of gestation has been correlated with an increase in the rates of neonatal intensive care unit admissions, macrosomia, shoulder dystocia, postmaturity syndrome, stillbirths and neonatal mortality. As for the mother, perineal lacerations, infections, postpartum haemorrhage (PPH) and caesarean delivery rates also appear to increase.

The American College of Obstetricians and Gynecologists (ACOG) states that initiation of antepartum surveillance at or beyond 41 gestational weeks may be indicated, the Society of Obstetricians and Gynaecologists of Canada (SOGC) recommends twice-weekly assessment of foetal well-being after 41 gestational weeks and *National Institute for Health and Care Excellence* (NICE) recommends surveillance from 42 weeks of gestation at least twice weekly [1].

Prelabour Rupture of Membranes (PROM): The ACOG and NICE recommend IOL at 34 gestational weeks in cases of preterm PROM, whereas SOGC at 32 gestational weeks if foetal lung maturity can be documented. Additionally, ACOG, SOGC and WHO recommend IOL in cases of PROM at term and NICE states that all women with PROM at term should be offered a choice of IOL with vaginal prostaglandin E2 (PGE2) or expectant management [1].

Vaginal Birth after Caesarean Delivery: Induction of labour in order to attempt vaginal birth after caesarean delivery remains an option according to ACOG, SOGC and NICE whereas WHO makes no recommendation. In such cases, ACOG and WHO recommend against the use of misoprostol, whereas SOGC states that no prostaglandins should be used. The ACOG states that it is difficult to make recommendations regarding PGE2, whereas NICE states that women with previous caesarean delivery may be offered IOL with vaginal PGE2, considering the woman's circumstances and wishes [5].

Foetal Death/ suspected intrauterine growth restriction: Regarding the optimal pharmacological method of IOL in cases of foetal death, ACOG recommends management according to the usual obstetric protocols (misoprostol, oxytocin), NICE recommends oral mifepristone followed by vaginal PGE2 or vaginal misoprostol and WHO recommends oral or vaginal misoprostol [1].

The Cervix and Cervical Ripening Process

In order to understand the cervical ripening process and how different cervical ripening methods work, it is important to review the different components of the cervix since different ripening methods target different components. The ground substance of the cervix includes proteoglycans (strengthen the cervix), glycosaminoglycans (help to soften the cervix), fibrillary collagen and matricellular proteins. The fibrous component of the cervix includes collagen (mostly Type I and Type III), elastin and reticulin and the cellular components of the cervix include fibroblasts and mast cells. There is minimal smooth muscle within the cervix. Many of the cervical ripening processes that occur incorporate breakdown or rearrangement of these cervical components. During the cervical ripening process there is an increase in vascularity as well as in stromal and glandular hypertrophy. There is inflammatory infiltration and production of cytokines that lead to metalloproteases being released which subsequently degrades collagen and leads to cervical change. Additionally, there is a decrease in proteoglycans in the extracellular matrix and an increase in glycosaminoglycans. Furthermore, there is a decrease in the crosslinks between collagen helices that leads to stromal breakdown and collagen rearrangement [6].

The best predictor for a successful IOL is cervical status, an unripe cervix conveys a lower likelihood of vaginal delivery [3, 6]. Cervical status is assessed using the Bishop score. First developed in 1964, the Bishop score is comprised of 5 parameters (dilatation, effacement, station, position and consistency of the cervix) and each cervical evaluation may have a maximum score of 13 [1]. In general, a Bishop score of ≤6 is considered unfavourable and cervical ripening should be considered prior to the initiation of oxytocin. For women with a Bishop score >8, the probability of a vaginal delivery after an induction is similar to if the woman presenting in spontaneous labour [6]. Cervical ripening, the process where the cervix becomes softened and ready for the onset of labour, occurs with both spontaneous labour and iatrogenic initiation of labour [6].

Methods of Cervical Ripening

Hippocrates first described methods for induction of labour (IOL) through mammary stimulation and mechanical cervical dilation. From the second century ad onward, practitioners have used methods such as artificial rupture of membranes and manual dilation of the cervix. More recent developments, including medications and mechanical devices, have offered providers increasingly effective means of inducing labour [1]. IOL can be either medically indicated or elective. Elective IOL refers to those that are performed in the absence of medical indications for reasons such as convenience, logistics or patient or provider preference. Medical indications for IOL include conditions for which the benefits of expediting birth outweigh the risks of continuing the pregnancy [1].

Before commencing IOL, all women should be informed about the indications of IOL, the methods of induction and the associated risks, including failure of induction and the associated risk of caesarean delivery. It should be noted that, in cases of IOL, progress of labour differs from cases with a spontaneous onset of labour [1]. The ideal methods for cervical ripening are those that are safe to both the mother and foetus, incur low cost, have minimal maternal discomfort and do not require extensive monitoring [3]. Cervical ripening methods include mechanical (e.g., intracervical balloon catheter; membrane sweeping and Laminaria etc.) and pharmacological methods (e.g., prostaglandins and oxytocin) as well as a combination of both mechanical and pharmacological methods [4].

Mechanical Methods

Membrane Sweeping*:* A simple method that is recommended by all guidelines as a way to reduce the need for other methods of IOL is membrane sweeping or striping. It involves the insertion of a digit past the internal os, followed by 3 circumferential passes of the digit causing separation of the membranes from the lower segment. This intervention causes significant increase in phospholipase A2 activity and PGF2a levels, increasing, in such a way, the likelihood of spontaneous onset of labour within 48 hours and reducing the need of induction with other methods. Compared with expectant management, an increased risk of vaginal bleeding and discomfort during vaginal examination was observed with sweeping of membranes [1].

Intracervical balloon catheter*:* Numerous studies have evaluated the safety and efficacy of the intracervical balloon catheter, which is thought to work through direct mechanical pressure that leads to dilation and the release of prostaglandin, which subsequently leads to stromal breakdown and an increased response to oxytocin. The intracervical Foley catheter has been shown to be associated with a decreased risk

of caesarean delivery when compared to oxytocin alone. When compared to prostaglandins, there is a decreased risk of tachysystole and foetal heart rate changes without a difference in caesarean delivery rates. Furthermore, there is no increased risk of infectious morbidity when an intracervical catheter is used among women with intact membranes. Because of minimal risks and favourable safety profile associated with the intracervical balloon catheter, many groups have determined the catheter to be the safest method for induction particularly in the setting where foetal monitoring is not available (e.g., in the outpatient setting or in countries with limited access to foetal monitoring). Additional advantages of the intracervical balloon catheter are its stability at room temperature and the inexpensive nature [4].

The literature supports the use of a single balloon intracervical catheter as it has been shown to be safer and less painful than the double balloon catheter. A 16-20F Foley catheter is used with a 30-60 mL of sterile water inflated into the 30 mL balloon. A higher inflation volume (>60 mL) has been associated with a higher dilation after catheter expulsion with some studies also demonstrating a shorter time to delivery. A recent meta-analysis found only a 2 h shorter time to delivery with 60 mL compared to 30 mL inflation amount. Sterile water is most often used to inflate the balloon. The balloon is placed either digitally or with a speculum. The deflated balloon is inserted past the internal os prior to inflating. The inflated balloon should sit at the level of the internal os. Once the catheter is in place, it can be taped to the inner thigh with tension [6].

Laminaria/Dilapan®: *Laminaria* and *Dilapan*® are two types of cervical osmotic dilators that are placed in the cervical canal to slowly open the cervix. Their mechanism of action is to absorb fluid from the surrounding tissue, progressively increasing their diameter over a 12-24 h period to achieve cervical ripening. *Dilapan*® was clinically introduced with the advantage over *Laminaria* of assured sterility, more ergonomic shape and superior dilating properties. *Dilapan* is a hygroscopic cervical dilator made from patented hydrogel, which leads to the absorption of fluid from cervical cells, thereby leading to cell membrane dehydration and softening along with mechanical dilation. The use of *Laminaria* has been abandoned in some high-income countries for concerns regarding postpartum infections [4]. Other complications associated with osmotic dilators include retention of the devices and anaphylaxis [3]. However, *Dilapan*® and other synthetic osmotic dilators for cervical ripening is a reasonable alternative for the induction of labour when other mechanical methods are not available, or the use of prostaglandins is contraindicated [4].

Pharmacological Methods

Prostaglandin E1: Synthetic prostaglandin PGE1, or misoprostol has been used for decades as a cervical-ripening agent and has been shown to decrease the risk of caesarean delivery when compared to oxytocin alone. There are many different dosing regimens and routes of administration for misoprostol with the most common and safe routes being vaginal or oral. Vaginal and oral doses range from 25 to 50 mg between 2 and 6 h. Lower doses are associated with less uterine hyperstimulation and foetal heart rate deceleration and are therefore preferable in settings where there is less frequent monitoring. When using the vaginal route, dosing intervals are more commonly q4-6 h, whereas with oral dosing they are shorter intervals, q2-4 h. The different intervals of dosing depending on the route of administration is due to differences in pharmacokinetics of prostaglandins with a shorter duration of action with oral misoprostol [4].

Prostaglandin E2: Prostaglandins are the most common form of pharmacologic cervical ripening methods. Prostaglandin E2 (Dinoprostone) is the only prostaglandin that is FDA approved for cervical ripening. Prostaglandin E2, or dinoprostone, comes in many preparations; however, it is most commonly used as Prepidil (0.5 mg dinoprostone per 3 g syringe) administered intracervically and repeated every 6-12 h and Cervidil (vaginal insert containing 10 mg dinoprostone in a timed-release formulation) and placed vaginally for 12 h. Compared to Prepidil, higher rates of vaginal delivery in 24 h has been demonstrated with Cervidil with no difference in caesarean. Disadvantages of both of these prostaglandin preparations are the need to keep refrigerated, they work over a long period of time (6-12 h compared to 3-4 h with prostaglandin E1) and they are expensive [6].

Oxytocin: Oxytocin is a peptide hormone produced in the hypothalamus and acts on myometrial smooth muscle. Oxytocin is a common agent used for induction but does not have any cervical ripening properties given the lack of smooth muscle within the cervix itself. Oxytocin is traditionally administered intravenously, particularly in the setting of induction and labour augmentation. Numerous studies have demonstrated that oxytocin alone has a lower rate of vaginal delivery compared to cervical-ripening agents including mechanical methods and prostaglandins [4]. Despite strong evidence on the use of misoprostol and other prostaglandins, there is widespread use of oxytocin alone as an induction agent [2].

Other methods

Amniotomy: Amniotomy is the artificial rupture of membranes and has been shown to expedite delivery in women presenting with spontaneous labour; although data are limited regarding amniotomy alone as a labour induction method, particularly in the setting of an unfavourable cervix. However, there are data regarding amniotomy timing during labour induction when other agents such as oxytocin or cervical-ripening agents are already being used that suggest a faster time to delivery with amniotomy earlier in the labour process [4].

Regarding methods of breast stimulation, sexual intercourse, herbal supplements, acupuncture, homeopathy and other similar methods, there is insufficient evidence in recommending those methods for IOL [1].

Complications/Risks of IOL

Concerns about the safety for women and newborns secondary to IOL include the effects of excessive uterine activity; a potential increase in the rate of caesarean; increased risk for postpartum haemorrhage (PPH); and adverse effects on the newborn such as foetal intolerance of labour, infection and respiratory distress syndrome. There is a considerable body of literature regarding adverse perinatal outcomes associated with IOL; however, it is often difficult to distinguish causation from association due to the methodological weaknesses of existing research [5].

Uterine Tachysystole: Excessive uterine activity can occur

during spontaneous or induced labour and with any of the pharmacologic methods used for IOL. Results of tachysystole for the foetus can include hypoxia, acidemia, acidosis, brain damage, or death if the tachysystole persists uncorrected. Foetuses at increased risk for acidemia secondary to growth restriction, infection, other complications are particularly vulnerable. Uterine rupture, although rare, is a possible maternal complication of tachysystole [5].

Increase in Caesarean sections: Increased rates of caesarean have frequently been cited as an undesirable effect of IOL, but the evidence for a causal relationship is uncertain because in many cases the same conditions for which IOL is indicated can independently increase the likelihood of caesarean [5].

Postpartum Haemorrhage (PPH): Evidence about the risk of PPH among women whose labour is induced is limited. In a study of otherwise low-risk women, IOL increased the risk of PPH and severe PPH. One systematic review concluded that there is insufficient evidence to determine whether IOL increases the risk of PPH [5].

Effects on the Newborn: Concerns for newborn complications resulting from IOL have focused on gestational age at the time of birth. Morbidity and mortality are both higher for infants born before 39 completed weeks' gestation. Neonatal mortality is higher at 37 weeks' and 38 weeks' than at 39 weeks' gestation. Morbidity is also significantly higher for newborns before 39 weeks' gestation. Birth between 37 and 39 weeks' gestation is associated with a 2 times higher rate of neonatal intensive care unit (NICU) admission. Newborns born at 37 weeks' gestation are also at higher risk for respiratory distress syndrome than those born after 39 weeks' gestation. Additional increased risks include sepsis, transient tachypnea of the newborn, pneumonia, ventilator use, hypoglycemia, cerebral palsy and developmental delays [5].

It is difficult to distinguish between the risks of IOL per se and the risks associated with early birth with the conditions for which IOL may be medically indicated. Based on what is known about the risks of IOL, it does appear that in the presence of maternal or foetal conditions known to increase the risks of continuing pregnancy, the risks of IOL are marginal and/or manageable [5].

Conclusion

Induction of labour is a common obstetric intervention associated with potential risks for the mother and the foetus/neonate and should be performed only when there is a clear medical indication to expedite delivery. The process of cervical ripening is complex with many different steps that lead to cervical remodelling. Different cervical ripening methods target various aspects of the biochemical processes to achieve cervical remodelling. There are both mechanical and pharmacological cervical ripening methods that can be used alone or in combination. Elective IOL should only be performed in rare or extraordinary circumstances and only when it would be beneficial to the mother and not cause harm to the newborn.

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