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Original Research Article

COMPREHENSIVE SYSTEMATIC REVIEW OF PHARMACOLOGICAL INTERVENTIONS FOR LABOR INDUCTION: MECHANISMS, EFFICACY, AND SAFETY

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Abstract

The process of artificially triggering the uterus to begin labor is known as induction of labor. The pregnant woman is typically given oxytocin or prostaglandins, or the amniotic membranes are manually ruptured, to carry out the procedure. The woman's mobility is restricted during induction of labor, and the procedure itself may be uncomfortable for her. The mother and her baby must be closely watched during the procedure to minimize any potential risks. There are pharmacological and mechanical methods for starting labor. Prostaglandins have frequently been used for labor induction, especially if the cervix is not favorable. Non-pharmacological methods include mechanical techniques like digital stretching of the cervix and sweeping of the membranes, hygroscopic cervical dilators, balloon catheters, artificial rupture of the membranes, and nipple stimulation. Pharmacological methods include oxytocin, prostaglandin (PG) analogs, and smooth muscle stimulants like herbs or castor oil. The infant who is exposed to opiates or other addictive substances during intrauterine development is at risk for postpartum withdrawal as well as long-term issues linked to drug side effects and frequently unfavorable social situations.

INTRODUCTION

The procedure of artificially stimulating the uterus to induce labor is known as induction of labor. The frequency of labor induction to reduce the gestational period has increased throughout the past few decades.[1] It is primarily because there are increasing findings highlighting the dangers to the fetus of a pregnancy lasting longer than 41 completed weeks of gestation. There are pharmacological and mechanical techniques for inducing labor. Vaginal prostaglandin E2 is the form of labor induction that is advised for the vast majority of female patients. The typical human cervix is around three and a half centimeters long and primarily made of collagen and 10 to 15% smooth muscle. In order to trigger the start of labor and enable dilatation, the cervix must go through a number of alterations. Cervical ripening is the process through which the cervix becomes flexible and soft as a result of a number of various metabolic events.[2] Induction of labor is often used to try to prevent issues or outcomes including cesarean sections, extended labor, postpartum hemorrhage, and traumatic births, as well as to enhance health outcomes for mothers and their babies.[3] Bishop score, parity (previous vaginal delivery), BMI, mother age, projected fetal weight, and diabetes are all factors that have been demonstrated to affect the success rates of induction. Cervical dilatation is the Bishop Score criterion that most accurately predicts a successful induction, followed by effacement, station, and position.[4] The physician should look carefully over the rationales for terminating the pregnancy and obtain informed consent before initiating labor induction. The mother and fetus should both receive a thorough examination, and fetal pulmonary maturity should be recorded if applicable.[5]

Prostaglandins

Prostaglandins are a type of 20-carbon polyunsaturated fatty acid compound that is a type of arachidonic acid derivative. Arachidonic acid undergoes significant changes through the cyclooxygenase (COX) pathway to yield prostaglandin G/H.[6] Prostaglandins are crucial for cervical ripening, labor induction, rupture of the fetal membranes, and uterine contraction. The cervical

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ripening effects of natural prostaglandins can be mimicked by synthetic prostaglandins.[7] Misoprostol (PGE1) and dinoprostone (PGE2) are two examples of synthetic analogs of naturally occurring prostaglandins that are used for their biological action.[8]

1. Misoprostol

Misoprostol is a synthetic PGE1 analog that continues to grow in importance in obstetrics and gynecology due to its capacity to both ripen the cervix and trigger uterine contractions.[7] Misoprostol causes edema of the mucosa and submucosa, which thickens the mucosal bilayer. This reduces hydrogen ion backflow and improves control of mucosal blood flow, which ultimately preserves the mucosa's capacity to produce new cells. Prostaglandin binds to smooth muscle cells in the uterine lining, causing uterotonic actions that include the capacity to induce labor and cervical ripening in addition to its abortifacient effects. Collagen breakdown in the stroma's connective tissue and a decrease in cervical tone brought on by stronger and more frequent contractions are the main causes of cervical dilatation. In addition, its uterotonic characteristics are effective in reducing postpartum hemorrhage.[9]

The mode of administration affects the pharmacokinetics of Misoprostol. Misoprostol is promptly and extensively metabolized in the liver after being administered orally into its main active metabolite, misoprostol acid (MPA). In 15 minutes, the plasma concentration reaches its maximum. The oral dose of Misoprostol needs to be twice as much as the vaginal dose to match the biologic activity equivalent to vaginal administration. Therefore, if 25 mcg is thought to be the ideal vaginal dosage, the ideal oral dose would be 50 mcg.[7] Misoprostol is found to be more effective than other prostaglandin agents and oxytocin. Due to its easy availability and inexpensiveness, it remains the most preferred agent for labor induction.[10]

2. Dinoprostone

Dinoprostone is a synthetic substance that is physically and chemically similar to PGE2, a substance that occurs naturally and acts as a local hormone. The majority of bodily tissues contain mild levels of endogenous PGE2. For cervical ripening prior to labor induction, dinoprostone formulations like endocervical gel, vaginal tablets, and vaginal inserts are authorized in lots of countries. It induces uterine contractions in a number of ways, including by increasing the synthesis of endogenous prostaglandin F2α and sensitizing the myometrium to the effects of either endogenous or exogenous oxytocin.[11]

It arrives in two different formulations: a cervical gel (Prepidil) and a vaginal insert (Cervidil). With a half-life of roughly 2.5 to 5 minutes, dinoprostone provides a prolonged and controlled onset of action and duration of effect. The cervical gel releases dinoprostone more quickly than the vaginal implant, but both formulations require cold storage to keep the substance chemically stable. As a result, the Dinoprostone vaginal insert offers a longer duration of action and a more gradual rise in plasma PGE2 levels.[12] The safety of misoprostol and dinoprostone is similar.[13]

For women trying a vaginal birth after a cesarean (VBAC), dinoprostone is contraindicated. The uterine rupture occurred in 2.5% to 3.9% of women trying a VBAC while using Dinoprostone for IOL, as compared with 0.45% to 0.7% of these women who went into spontaneous labor.[7]

Oxytocin

The hormone that is most associated with uterine contractions during labor is oxytocin. The number of oxytocin receptors rises to 300-fold over the course of pregnancy. The hypothalamus produces oxytocin, which is then stored in the posterior pituitary gland.[14] By inducing G-protein-coupled receptors to trigger an increase in intracellular calcium in uterine myofibrils, oxytocin stimulates uterine contractions in the myometrium. Numerous signals that induce uterine contraction by raising intracellular calcium levels are produced when the oxytocin receptor is activated. It induces uterine contractions, which in turn trigger the production of additional oxytocin. This increases contraction frequency and strength, allowing a mother to deliver her baby vaginally without assistance. Additionally, oxytocin possesses vasodilatory and antidiuretic properties that increase cerebral, coronary, and even renal blood flow.[15]

In the literature, numerous dose plans for oxytocin have been suggested. The American College of Obstetrics and Gynecology (ACOG) recommends a low-dose regimen with gradual increases of 1 to 2 mU every 15 to 40 minutes, starting at 0.5 to 2 mU/min. A high-dose regimen is advised to start at 6 mU/min and increase by 3 to 6 mU every 15 to 40 minutes. Making a solution of 30 units of oxytocin in 500 mL of crystalloid is a typical method for getting the infusion pump setting (milliliters per hour, or mL/h) to match the dose given (mU/min). The plasma half-life of oxytocin is about 3 to 6 minutes, which is relatively short. Within 3 to 5 minutes, there is a uterine reaction, and after 40 minutes, plasma levels are constant.[16] According to the results of many random control trials, it has been found that Oxytocin is far more effective than PGE1 and PGE2 in producing myometrial contractility.[17]

Membrane Sweeping

During a vaginal examination, membrane sweeping is done with the patient's permission. The procedure refers to the physician introducing one or two fingers into the woman's cervix and using a circular motion to separate the inferior pole of the membrane from the lower uterine segment. By releasing localized prostaglandins F2, phospholipase A2, and cytokines from the intrauterine tissues, membrane sweeping can help promote the physiologically proper commencement of labor. These hormones affect the cervix in a way that promotes cervical ripening and can lead to uterine contractions.[18] It is intended to encourage spontaneous labor in order to minimize the

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demand for formal induction of labor in postmaturity.[19]

In a series of reviews on labor induction techniques, it was not demonstrated that sweeping the membranes had any positive effects on the key outcomes. Women in the sweeping group experienced discomfort during the intervention, bleeding, and irregular contractions, but the frequency of serious adverse effects did not increase.[20]

When compared to vaginal PGE2 and vaginal misoprostol, mechanical approaches for inducing labor were associated with lower rates of uterine hyperstimulation, but they also raised the risk of maternal and infant infectious challenges.[21] When compared to membrane sweeping, patients who received a single dose of oral Misoprostol had a shorter latency period, less need for oxytocin augmentation, and shorter labor times.[22] Membrane sweeping seems to have the most solid scientific support of non-pharmacologic techniques.

Without increasing risks that are clinically significant, it was successful in lowering post-term pregnancies.[21] Membrane sweeping is a safe and effective treatment that lowers the rate of labor induction by reducing the prevalence of post-mature pregnancies.[23]

Foley Catheter

The goal of labor induction is to induce vaginal birth by inducing uterine contractions with a variety of pharmacological and mechanical techniques. While pharmacological approaches include oxytocin, prostaglandins, and antiprogestins like mifepristone, common techniques for labor induction include transcervical Foley's catheter with or without additional amniotic saline infusion, cervical stretching, and amniotomy.[24] In addition to ripening the cervix, prostaglandins can promote myometrial contractility, which may result in tachysystole. Mechanical techniques are frequently employed to induce labor and ripen the cervix in order to reduce adverse outcomes.[25] The Foley's catheter is considered an appropriate induction agent by the American Congress of Obstetricians and Gynecologists due to its excellent efficacy and safety, as well as its advantages of being less expensive, stable at room temperature, and having a lower risk of tachysystole than drug therapies.[24]

a) Transcervical Foley Catheter

In all clinical settings, the aim is to induce labor as quickly as possible; the cervical ripening time needs to be taken into account while selecting a ripening technique. Therefore, the limited uterine activation generated by the mechanical devices employed for cervical ripening is definitely helpful.[26] An unfavorable cervix increases the risk of prolonged labor and increases the likelihood of cesarean sections after labor induction. When inducing labor in women who have had a previous cesarean section and are at a greater risk of uterine rupture, the Foley catheter, which has no known risk of hyperstimulation, may be especially valuable.[27]

b) Transcervical-amniotic Foley catheter

Extraamniotic saline infusion is added to the Foley catheter to encourage endogenous prostaglandin release by purging the membrane and by applying more mechanical stress. A significant induction-to-delivery interval would be shortened for women undergoing labor induction in the presence of an unfavorable cervix if extraamniotic saline infusion were added to the Foley catheter alone, according to the results of a large randomized clinical trial comparing the transcervical Foley catheter with extraamniotic saline infusion for labor induction and cervical ripening in women with an unfavorable cervix.[28]

Combined Pharmacological Approaches

Given that labor induction continues to remain a prevalent practice, it's crucial to enhance the currently available safe and efficient agents. The ideal drug shortens labor without affecting the health of the mother or the fetus. Clinicians must weigh potential problems against the benefit of a faster birth. The clinician's preference and the existence of contraindications determine the agent to be used for cervical ripening and induction.[29] Combining oxytocin with dinoprostone decreased the time from induction to delivery and increased the proportion of vaginal deliveries without having any negative effects on the fetus or the mother.[30]

Misoprostol is a more powerful medication that frequently causes the beginning of contractions that result in labor. Within 24 hours of the Misoprostol vaginal insert being placed, labor often begins, and the patient will deliver the baby. Patients who take Dinoprostone further require excess oxytocin to complete delivery. The delivery happened dynamically before 24 hours for patients who took Misoprostol, making the addition of oxytocin mostly unnecessary. However, for the patients who receive Dinoprostone, oxytocin was added, and delivery occurs peacefully, primarily after 24 hours but still within 48 hours.[31]

Pharmacological Agents in Special Population

a) Patients with prior cesarean sections or uterine scars

A uterine rupture is a rare occurrence. It is significant since major peripartum hysterectomy, serious maternal morbidity, and fetal mortality continue to be related to it.[32] Induced labor in women with prior low transverse cesarean sections may be linked to uterine rupture rates that are comparable to those associated with natural labor. Misoprostol has consistently been linked to an unacceptably high rate of uterine rupture when used for labor induction in patients with scarred uteruses, and it is not used in these situations. Hence Oxytocin alone can be the best agent in this type of situation.[33]

b) Gestational diabetes and hypertension

The pathophysiology of gestational diabetes mellitus is characterized by peripheral insulin resistance and declining beta-cell function. The use of regular insulin during pregnancy poses limitations. In pregnancy to treat gestational diabetes mellitus, new

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insulin analogs such as insulin lispro, insulin aspart, insulin glulisine, insulin glargine, and insulin detemir found greater advantages.[34] A novel therapeutic strategy that includes Myo-inositol dietary supplementation during pregnancy has been shown to be successful in both preventing and treating gestational diabetes mellitus.[35]

The most common medical conditions in pregnancy are hypertensive disorders. Both the expectant mother and the fetus are affected by it. Maternal mortality is primarily caused by severe cases of hypertensive disorders of pregnancy, such as eclampsia. The vascular endothelium becomes activated and dysfunctional as a result of noxious placental factors released by ischemic changes and toxic radicals produced by oxidative stress. Endothelium that has been damaged or activated secretes chemicals that increase coagulation and vasopressor sensitivity. These complications are reduced when pregnancy-related hypertension is managed with antihypertensive medications. Adrenoceptor antagonists (nifedipine, methyldopa, and labetalol) are the most commonly used antihypertensive medications during pregnancy.[36]

Maternal and Neonatal Outcomes

Prenatal exposure to both legal and illegal psychoactive substances can result in physiological and/or neurobehavioral issues in the newborn that can lead to issues with feeding, sleeping, moving around, having the ability to interact with others, and generally having a poor neonatal adaptation process.[37] As long as anti-epileptic medications must be taken while pregnant, no completely safe dosage will offer therapeutic efficacy without running the risk of causing structural or developmental defects in the exposed infant. Another crucial aspect of managing patients who are pregnant is to try to stay out of polytherapy whenever possible. The developing embryo is more at risk for craniofacial malformations when two or more anti-epileptic drugs are prescribed.[38]

Antidiabetic medications are increasingly prescribed to pregnant women with gestational diabetes mellitus (GDM) or polycystic ovary syndrome (PCOS) to treat hyperglycemia. There is evidence that suggests maternal metformin use during pregnancy results in heavier children than normal.[39]

Comparative Analysis

Non-parametric cesareans are advised if the time to vaginal birth is the chosen effective outcome in labor induction. Results from the established dinoprostone vaginal gel protocol for cervical ripening and induction, low-dose vaginal misoprostol, and oral misoprostol (50 mg po q4h prn) showed no statistically significant differences in outcomes. Depending on cost, regional logistics, and patient preferences, clinicians can choose between these induction agents.[40]

Table 1: Overall table for comparison of pharmacological methods

Cervical ripening method	Routes of administration	Dose options	Tips for optimal use
PGE1 analog, Misoprostol	Oral, buccal, vaginal	25-50 mcg every 6-8 hr	When compared to dinoprostone, it results in shorter labor times in nulliparous people without increasing uterine hyperstimulation or meconium-stained amniotic fluid. Only those with a Bishop score of >4 after the first dose or multiparous individuals should use a single-dosing regimen prior to the start of oxytocin therapy. If available, oral solution (25 mcg every 2 hours) is preferable to dinoprostone or oxytocin for reducing the likelihood of cesarean delivery without raising the incidence of uterine hyperstimulation. In women with intact membranes, buccal administration is less effective than vaginal administration for reducing labor duration, preventing cesarean birth, and improving the fetal status. Not suitable for people who have had uterine surgery in the past.
PGE2 analog, Dinoprostone	Vaginal insert (10mg), Cervical gel (0.3mg/hr)	Vaginal insert – 12 hr, Cervical gel – every 6 hr	When there are concerns about the fetal tolerance of contractions, dinoprostone in the form of a vaginal insert may be preferred over vaginal misoprostol tablets or oral dosing (cervical balloons are another option in these circumstances). Not suitable for people who have had uterine surgery in the past.
Cervical balloons	Intracervical	30 – 90 ml	Cervical balloons are best for outpatient cervical ripening or for individuals who want a vaginal birth after cesarean because of their localized action, absence of systemic side effects, and simple discontinuation.
Oxytocin	Intravenous	Depends upon individuals.	Not advised as a stand-alone treatment for cervical ripening unless there has been a previous cesarean delivery or there are other reasons why prostaglandins or cervical balloons are not supposed to be used.[41]

When compared to Dinoprostone, the PGE1 analog Misoprostol shortens the length of labor. It is available orally, buccally, and vaginally. When compared to the other two routes, the buccal route is less effective in all three. While Dinoprostone, which is superior to Misoprostol tablets, is only offered as a vaginal insert or cervical gel, Effective local action is provided by the cervical balloons for successful

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labor. When misoprostol is combined with a cervical balloon, cervical ripening occurs more quickly than when it is used alone, which reduces the time needed to induce labor.[41] In general, misoprostol and oxytocin with amniotomy (for women with a good cervix) are more effective than other agents at causing VD within 24 hours. The order of the various methods in terms of safety was less obvious. According to the cost-effectiveness analysis, buccal or sublingual misoprostol had the lowest cost, while titrated (low-dose) oral misoprostol solution produced the highest utility.[42]

CONCLUSION

Induction of labor is more prevalent nowadays. Many pharmacological and mechanical methods are available to induce labor. Clinicians should choose the ideal method for every individual patient depending on their cervix conditions, comobitidites, and other past medical histories. Induction of labor occurred in nearly half of nulliparous women and in 4 of 10 multiparous women who attempted vaginal delivery in a modern obstetrics setting. By gestational age and parity, precursors varied, and vaginal delivery was more successful in straightforward pregnancies. Despite the fact that there is evidence to suggest that neonatal morbidity and mortality decrease with each gestational week until 39 weeks of gestation, about 1 in 10 preterm inductions did not indicate induction or another pregnancy condition. The efficacy of various pharmacological and mechanical methods is discussed in detail in this article, and a clinical setting, clinicians should make rational decisions about what type of method to implement to handle the situation correctly.

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