Induction of labor—Pharmacology methods

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Abstract

Pharmacologic methods for induction of labor have been used for many decades. Pharmacologic agents have an advantage over mechanical methods in that they can be used during both the initial cervical ripening stage of induction and throughout the second stage of labor. Pharmacologic induction agents such as prostaglandins and oxytocin are commonly used for labor and delivery floors and are well established for use in cervical ripening. Nitric oxide donors and mifepristone are known agents in medicine but are new and actively studied in the area of cervical ripening. These agents are introduced and analyzed in this review.

Introduction

Pharmacologic methods for cervical ripening and labor induction have been used for decades as a method to manage the timing of labor. While more cost-effective mechanical methods are currently available, there are many patients for whom pharmacologic agents, such as prostaglandins, mifepristone, and nitric oxide donors, are preferable. Unlike mechanical agents, these pharmacologic agents may be favored due to their availability for both pre-induction cervical ripening and for the duration of the induction of labor.

Prostaglandins

Background

Prostaglandins are a group of cyclic fatty acid compounds that are found in many different tissues throughout the body. Prostaglandins act on a variety of receptor types and therefore have different responses produced depending on the receptor on which it is acting. The role of prostaglandins in obstetrics was first established in the 1970s. Prostaglandins both increase uterine smooth muscle contractility and aid in cervical ripening. Common side effects with the use of prostaglandins can be attributed to their role in other tissues that contain prostaglandin receptors. Side effects include transient fall in blood pressure, nausea and vomiting, and fever.

Mechanism of action

Prostaglandin E2, or dinoprostone, is a common agent used in labor induction. It effects are twofold, both initiating uterine contractions and softening the cervix. The exact mechanism of action in cervical ripening is unknown but is thought to be partially due to a reaction of locally administered dinoprostine causing collagen degradation secondary to the secretion of collagenase.

Availability

Dinoprostone is available as Prepidil, Cervidil, and Prostin E2. Prepidil is an intracervical prostaglandin E2 gel whereas Cervidil is a controlled-release hydrogel pessary, and Prostin E2 is a vaginal suppository. A study performed by Chyu et al.1 showed that both Cervidil and Prepidil are effective in achieving cervical ripening when compared with placebo but that Cervidil achieves ripening over a shorter period (11.1 hour versus 15.2 hour, p < 0.001). Although the market...
price of prepidil is about $25 less than that of cervidil, because the time to achieve vaginal delivery is shorter and the use of oxytocin is less frequent, the overall cost is expected to be less with the use of Cervidil as compared with Prepidil.

Data

Prostaglandin is a preferred method of cervical ripening in many institutions. There is mixed data on prostaglandin versus mechanical methods for cervical ripening. In a study by Rayburn prostaglandin E2 was found to be superior to placebo in increasing cervical Bishop scores, reducing induction failures, and lowering rate of cesarean sections. In a study comparing dinoprostone and a mechanical method of cervical ripening, the Foley catheter was found to have a higher failure rate and higher chance of needing additional oxytocin. Comparable outcomes were found between the 2 for mean induction time and cesarean section rate. Contrarily, in a study by Sciscione et al., dinoprostone resulted in lower Bishop scores and a longer induction time when compared with Foley bulbs. Lastly, when compared with misoprostol, patients using prostaglandin E2 were found to have a decreased chance of achieving active phase, a longer induction time, and a higher risk for cesarean section.

Progesterone receptor antagonists (mifepristone)

Background

Progesterone plays an integral part in all stages of pregnancy, from conception to labor. Throughout pregnancy, progesterone acts to inhibit smooth muscle contraction of the myometrium and studies have suggested a role in maintaining the structural integrity of the cervix. At the initiation of labor, a progesterone withdrawal is essential. In this aspect, progesterone receptor antagonists may be useful in the induction of labor, acting as a synthetic method to a progesterone withdrawal. Mifepristone should not be used in patients with hemorrhagic disorders or patients who are on long-term corticosteroid therapy due to mifepristone’s high relative binding affinity to the glucocorticoid receptor.

Mechanism of action

Mifepristone is a steroidal anti-progesterone and anti-glucocorticoid synthetic drug. In the presence of progesterone, mifepristone acts as a competitive receptor antagonist.

Availability

Progesterone receptor antagonists are sold in the United States under the name Mifepristone (Mireprex). During early trials, it was known as RU-38486 or simply RU-486. The United States FDA has approved the use of this drug for medical termination of intrauterine pregnancies up to 49 days. Mifepristone is given orally at the time of desired induction.

Data

Studies have shown that mifepristone is superior to placebo for cervical ripening. In a study by Athawale et al., mifepristone was found to have a 76% rate of successful vaginal delivery versus 36% in the placebo group and the chance of requiring augmentation with misoprostol or oxytocin was significantly decreased when compared with the placebo. In a study of patients undergoing second trimester terminations, mifepristone and misoprostol were shown to have significant decrease in delivery time when compared with laminaria and misoprostol (mean of 10 hour versus 16 hour, respectively).

Oxytocin

Background

Oxytocin is best known in labor as the hormone that is directly related to uterine contractions. As pregnancy progresses, the number of oxytocin receptors increases by as much as 300-fold. On the initiation of labor, oxytocin is released and acts on the uterus to produce contractions that increase in frequency and strength as labor progresses. Synthetic versions of oxytocin have been used in labor induction for decades. Though better outcomes have been shown when oxytocin is used for induction with a favorable cervix, studies have shown a benefit to oxytocin use for cervical ripening when compared with expectant management. Patients should be informed of the risks of oxytocin use, which commonly include a failed induction and uterine tachysystole, and more rarely, uterine rupture.

Mechanism of action

Oxytocin is a peptide hormone produced by the hypothalamus and stored in the posterior pituitary gland. Outside of labor, it is best known for its role in breast milk ejection. In labor, oxytocin is released from the posterior pituitary gland and acts on the uterus at the level of the myometrial smooth muscle cell. Oxytocin acts on a G-protein-coupled receptor that activates a signaling pathway to increase the concentration of calcium within the smooth muscle cell leading to a contraction. Oxytocin has not been shown to have a direct effect on the cervix.

Availability

Oxytocin is available as Pitocin™, a synthetic version of the hormone. Pitocin is given as a starting dose ranging from 1 to 2 mU/minutes. It is increased by 1–6 mU/minutes every 15–40 minutes. Protocols are typically established by individual hospitals.

Data

In a study by Alfrenvic et al., fewer women failed to deliver within 24 hour when using a oxytocin when compared with a placebo. Ferguson et al. showed that low-dose oxytocin alone was found to have a longer interval to delivery when
compared with misoprostol (66% versus 61%, respectively), but each drug was found to have a similar success rate of vaginal delivery. There was also a decreased rate of cesarean section for an indication of fetal intolerance in the oxytocin-only group versus the misoprostol group.

**Nitric oxide (NO) donors**

**Background**

NO donors have been used to induce cervical ripening in women who undergo a termination in their first trimester of pregnancy for many years. Recently, this compound has been studied in its use as a cervical ripening agent in term pregnancies undergoing an induction of labor. Studies have shown that nitric oxide metabolites are increased in cervical pregnancies undergoing an induction of labor. Studies have also examined the use of NO donors in cervical ripening. In a meta-analysis by Kelly et al., 10 trials were examined and it was found that there was limited data available and no evidence of any difference between NO donors and other induction agents. In another study by Bullarbo et al., 10 women treated with isosorbide mononitrate went into labor within 24 hour when compared with women in the placebo group (p < 0.05).

**Mechanism of action**

Nitric oxide is a free radical synthesized by the enzyme nitric oxide synthetase and has been noted in many physiological and pathophysiological processes in the human body. In all tissues, nitric oxide is a multifunctional molecule that participates in signaling. During pregnancy, NO is produced by the cervix and placenta. The mechanism by which NO works on smooth muscle tissue is such that it activates a signaling cascade to increase calcium efflux and inhibits the cross-bridge cycle of the myocyte. Studies have shown the presence of nitric oxide in cervical smooth muscle tissue, epithelial cells, and leukocytes within the cervix. 16

**Availability**

The commonly used nitric oxide donor in investigational studies was isosorbide mononitrate. In all studies, isosorbide mononitrate was given as a 40–80 mg vaginal dose.

**Data**

There is conflicting data on the efficacy of NO donors in cervical ripening. In a meta-analysis by Kelly et al., 10 trials were examined and it was found that there was limited data available and no evidence of any difference between NO donors and other induction agents. In another study by Bullarbo et al., 10 women treated with isosorbide mononitrate went into labor within 24 hour when compared with women in the placebo group (p < 0.05).

**References**