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Pharmacological Interventions in Labor and Delivery

Susan Wray,[1] Sarah Arrowsmith,[2] and Andrew Sharp[1]

[1]Women's & Children's Health, Faculty of Health & Life Sciences, University of Liverpool, Liverpool, United Kingdom; email: s.wray@liv.ac.uk

[2]Department of Life Sciences, Manchester Metropolitan University, Manchester, United Kingdom

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Abstract

While there is not a wide range of pregnancy-specific drugs, there are some very specific high-risk areas of obstetric care for which unique pharmacological approaches have been established. In preterm birth, labor induction and augmentation, and the management of postpartum hemorrhage, these pharmacological approaches have become the bedrock in managing some of the most common and problematic areas of antenatal and intrapartum care. In this review, we summarize the existing established and emerging evidence that supports and broadens these pharmacological approaches to obstetric management and its impact on clinical practice. It is clear that existing therapeutics are limited. They have largely been developed from our knowledge of the physiology of the myometrium and act on hormonal receptors and their signaling pathways or on ion channels influencing excitability. Newer drugs in development are mostly refinements of these two approaches, but novel agents from plants and improved formulations are also discussed.

INTRODUCTION

This short review focuses on the drugs available to help women during the different stages of labor and induction of labor (IOL) and with pain relief and threatened preterm labor. In each section we briefly outline the clinical need for therapeutics, review current pharmacological options and efficacy along with mechanism of action, and then make suggestions for where future developments may arise. What will become clear is how pivotal oxytocin, in a variety of formulations, is to many clinical scenarios, along with progesterone and prostaglandins (PGs), and how no successful breakthrough drugs have been developed. This lacuna points to the need for a more complete understanding of the complex interplay between genes, hormones, the uterine environment, mechanical factors, ion channels, signaling pathways, and the myometrium and how this drives gestational length and labor. **Figure 1** shows the main drugs discussed and their sites of action. **Figure 2** shows the pathways within the myometrial cell where uterine stimulants and relaxants act.

TERM LABOR

Most labors occur at term, with strong, frequent uterine contractions, leading to thinning (effacement) and dilation of the cervix in around 24 h, followed by delivery of the baby and placenta. Other than pain relief, as discussed below, most term labors proceed without pharmacological interventions. The contractions that give rise to the term labor arise from the smooth muscle cells in the myometrium that have increased in size, number, connectivity, and excitability as gestation advances (1–3). The cervix also softens and becomes amenable to shortening and effacement by

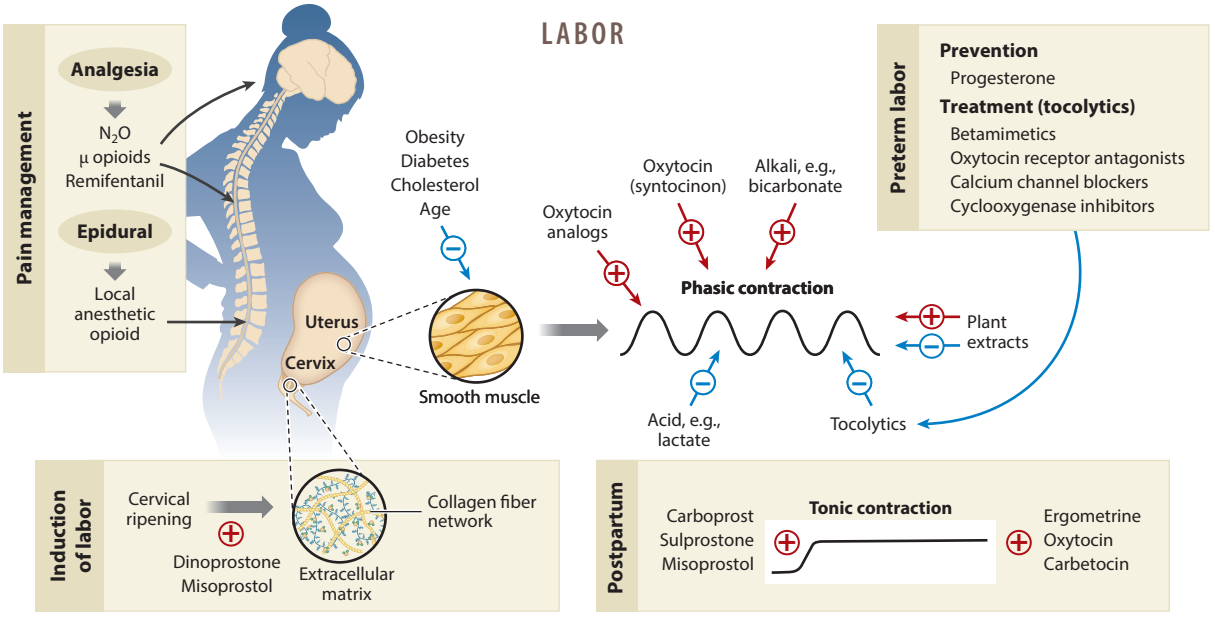

Figure 1

Schematic of the main uses of drugs in labor and their sites of action. Indirect effects on labor outcome can arise from medical conditions and the drugs used to treat them. Red plus signs and arrows indicate that the drug has a stimulatory effect on labor, and blue minus signs and arrows indicate that the drug or medical condition has a relaxatory effect on labor contractions or slows down their progression.

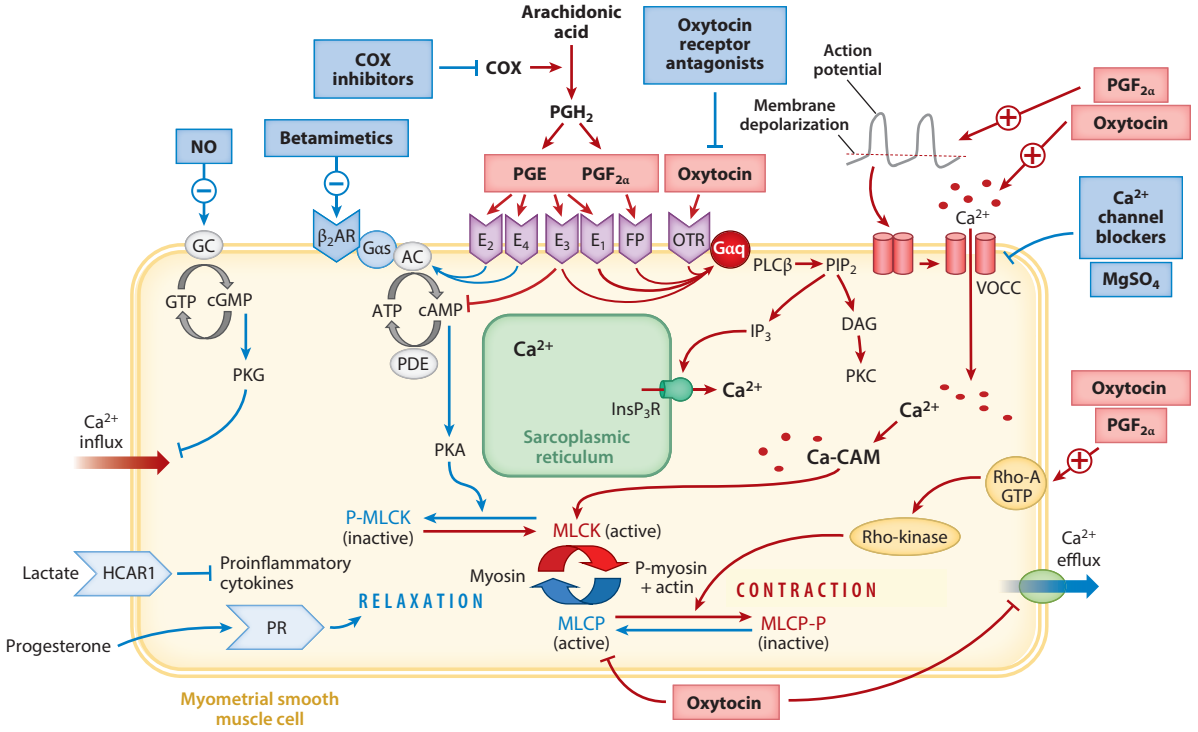

Figure 2

Mechanisms of action of uterotonics (oxytocin and prostaglandins) and tocolytics (*blue boxes*) in myometrial smooth muscle cells. Red plus signs, arrows, and bars show pathways that when activated lead to stimulation of contraction, while blue minus signs, arrows, and bars show pathways leading to suppression of contraction. Abbreviations: β_2AR, β2-adrenergic receptor; AC, adenylyl cyclase; ATP, adenosine triphosphate; Ca-CAM, calcium-calmodulin complex; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; COX, cyclo-oxygenase; DAG, diacylglycerol; E1–E4, prostaglandin EP1, EP2, EP3, and EP4 receptors; FP, prostaglandin F2α receptor; Gαs, G protein alpha (s) subunit; Gαq, G protein alpha (q) subunit; GC, guanylyl cyclase; GTP, guanosine triphosphate; HCAR1, hydroxycarboxylic acid 1 receptor; $InsP_3R$, inositol trisphosphate receptor; IP_3, inositol trisphosphate; $MgSO_4$, magnesium sulphate; MLCK, myosin light chain kinase; MLCP, myosin light chain phosphatase; NO, nitric oxide; OTR, oxytocin receptor; PDE, phosphodiesterase; PGE, prostaglandin E; $PGF_{2\alpha}$, prostaglandin F2 alpha; PGH_2, prostaglandin H_2; PIP_2, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; PLCβ, phospholipase C beta; PR, progesterone receptor; VOCC, voltage-operated calcium channel. Figure adapted from Reference 128.

the repetitive contractions that characterize labor. The feedback from hypothalamic release of the uterotonic hormone oxytocin drives labor forward to its expulsive climax, with delivery of the neonate and placenta.

However, around 10% of term labors do not progress well; the cervix fails to dilate adequately because the strength and/or frequency of uterine contractions is inadequate (4, 5). Such labors are referred to as dystocic (used in this review), hypotonic uterine inertia, or, simply, slow-to-progress/arrested labor. Labor can arrest due to anatomical reasons, for example, cephalopelvic disproportion, which is a condition that is more frequent in the developing world due to poor nutrition and young maternal age (6). In these circumstances, pharmaceutical stimulation of the myometrium would be unhelpful and potentially dangerous in overcoming the physical obstruction. This would also be the case when there is a malpositioned placenta or fetus, and these topics are not discussed further.

Dystocia

Functional dystocia, that is, that caused by problems with uterine contractions, is the major cause of unplanned (emergency) caesarean section (CS) (4). Being able to reduce this condition would free clinical and financial resources; avoid risks associated with surgery, such as infection and thrombosis and increased risks of a variety of conditions in the neonates; and reduce maternal trauma (7). Dystocia is diagnosed during the routine monitoring and management of labor, for example, by digital measurement of cervical dilation and time in labor. What constitutes latent versus active labor, what the normal rate of cervical dilation should be taken as, and how long and what cervical dilation should be used to define a labor as dystocic remain topics of debate and vary by region (8, 9). These details need to be considered when assessing the outcome of trials of successful interventions for dystocic labor. End points of trials also vary but are usually effect on CS rate, duration of labor, or neonatal status. In addition, first labors are naturally longer than subsequent labors, and maternal support during pregnancy and delivery can also affect the duration of labor (10).

Body mass index (BMI) and age are both important maternal factors to consider when assessing labor outcome (11). Obesity is increasing globally and can contribute to difficult labors; rates of induction, dystocic labor, and need for operative delivery are all increased (12, 13). These outcomes can be due to the associated comorbidities, for example, diabetes and hypertension, but research has also shown that elevated cholesterol, a common finding in obesity, affects signaling in myometrial cells (14), specifically, the signaling localized to caveolae, which are also known as lipid rafts (14, 15). These plasma membrane invaginations are rich in cholesterol, and disturbance to cholesterol levels affects the number of caveolae and efficacy of signal transduction located within them. Our group showed that increasing cholesterol decreases myometrial contractility, and conversely, reducing cholesterol increases contractility and excitability, as outward currents due to potassium channel conductance are increased (16). Thus, controlling lipid levels in pregnant women is important. However, the fetus has a high lipid requirement, which should not be compromised, and there are concerns around fetal development and miscarriage; statins are thus widely contraindicated (17).

Increased maternal age, especially for a first pregnancy, is also an independent risk factor for a more difficult labor (18). As with obesity, the effects of aging are likely to be multifactorial. In vitro studies have found changes in myometrial cells (19) and a continuum of decreased contractility in biopsies as women age (20). It should be noted, however, that the myometrium remains contractile beyond menopause (20). With assisted reproductive techniques, women in their 60s and 70s have given birth, showing that the ability of both the endometrium and myometrium to respond to hormones and mechanical factors (stretch) remains.

Oxytocin (Syntocinon)

If a decision to assist labor is made, then there is only one licensed drug that can be administered in an attempt to boost contractility: oxytocin (21). It is synthesized and marketed as Syntocinon, which, as noted below, is also used to induce labor and to prevent excessive postpartum bleeding. Syntocinon for labor augmentation is usually given intravenously (IV) via a pump so that speed and dose can be titrated in line with myometrial response. This stimulation is not without risk of uterine tachysystole or tetanic contraction. The resulting compression of the uterine vessels decreases placental perfusion, and subsequent fetal ischemia and distress can rapidly ensue (22–24). In rare cases, uterine rupture and fetal demise can occur with Syntocinon overdoses. For these reasons, bolus injections of oxytocin are contraindicated. In addition, studies of low- versus high-dose oxytocin regimes have concluded that the latter carries more risks, notably of tachysystole,

and does not decrease the time to vaginal delivery or reduce CS rates (25, 26). Unfortunately, it remains the case that around 50% of women will not respond to oxytocin, and there is no other pharmaceutical treatment available (27). Evidence strongly suggests that there are physiological reasons why the uterus does not always respond to Syntocinon, and a predictive test based on this has been developed, as discussed next.

Lactate, Sodium Bicarbonate, and Hydration

Individual studies and meta-analyses indicate that oxytocin does not reduce the need for emergency CS (21). One reason for this is suggested by metabolic and contractile data showing that the dystocic myometrium is in an exhausted state. There is local acidemia, related to increased lactate levels in women laboring dystocically (28). These changes have been shown in animal and human studies to be caused by the uterine contractions compressing embedded vessels and producing repeated transient hypoxic episodes (29, 30). Eventually the buildup of acid impedes calcium entry into the myocytes, and thus the myometrium is unable to produce strong contractions and labor stalls (31–33). Under these conditions, oxytocin does not effectively stimulate contractions, and CS delivery is required.

Increased levels of lactate can be found in the amniotic fluid and indeed are predictive of labors that will not benefit from oxytocin administration, and preparation for operative delivery can be counseled (34). Given this persuasive evidence that lactic acid is a key cause of dystocic labors, it was reasoned that administration of a weak alkaline should null the acidic changes and allow the myometrium to recover. This was tested initially in vitro by simultaneously applying lactate and ammonium chloride; without acidification, lactate no longer decreased force in the myometrial strips (35). This study was followed by a small, randomized control trial (RCT) of women in Sweden who had a clinical diagnosis of dystocia. The results showed a significant decrease in the number of operative deliveries in the women who drank water containing 10 g of bicarbonate (36). These results need to be tested in other populations, but if reproduced, they would provide an inexpensive alternate treatment for dystocia. Pharmaceutical preparations with different concentrations of bicarbonate, to account for BMI or cervical dilation, may produce the next personalized therapy for dystocia.

Other studies have focused on helping to prevent a buildup of metabolites such as lactate by keeping women well hydrated in labor. A systematic review of seven RCTs of IV fluid administration demonstrated a reduction in labor length and also a significant decrease in the incidence of CS at 250 mL/h but not 125 mL/h (37). An earlier review had not found such a difference in CS rates (38). The authors of the later study suggest they were able to demonstrate a significant difference as more trials with CS identified as a major outcome were included. Anecdotal reports from midwives have suggested that if dystocia occurs, but all indicators are otherwise satisfactory, allowing the mother to rest, and presumably the myometrium to metabolically recover, could be a successful option and warrants investigation.

Future Developments

It is a goal in many countries to reduce CS rates, especially those that are unplanned. More refined pharmaceutical interventions cannot rationally be developed without a better understanding of the causes of dystocia. The discovery of local lactic acidemia in women laboring dysfunctionally (28) was the first clinical and physiological insight into cause. That lactate concentration in amniotic fluid can predict labor outcome, and bicarbonate significantly reduces the rate of unplanned CSs, adds to the evidence that the cause of dystocia often lies within the uterus. However, whether the dysfunction lies with the uterine vessels or the myometrial muscle cells

not tolerating the rigors of labor is unknown (22). This calls for more research in this area. Interestingly, recent work has demonstrated that intracellular signaling can occur by extracellular lactate acting as an agonist at hydroxycarboxylic acid 1 receptors (HCAR1s, formerly known as G protein–coupled receptor 81) (39). Studies have indicated that the downstream effects of this novel signaling pathway are anti-inflammatory (40). Given the suggested links between inflammation and preterm delivery (see below), these data suggest a hitherto unknown role of lactate in the myometrium. Madaan et al. (41) demonstrated that extracellular lactate acting via HCAR1 decreased proinflammatory cytokines, and the use of 3,5-dihydoxybenzoic acid, an HCAR1 agonist, decreased endotoxin-induced preterm birth (PTB) in mice. These exciting findings do not appear to have been taken further—perhaps because there is little evidence in women that decreasing proinflammatory cytokines alone prevents PTB.

One cause of women not having a good myometrial response to Syntocinon may be that oxytocin receptors are desensitized. New agonists are being produced based on modifications to oxytocin, or its analogs such as inotocin (from the black garden ant, *Lasius niger*), to provide improved receptor binding, stability, and resistance to desensitization (42, 43). Some of these have been tested on animal models and human cells, but none appear to be in clinical development yet.

Many drugs have been developed from plants. Given the acute need for more and better drugs to help women suffering difficult labors, there is considerable interest in finding novel agents from plants to act on the myometrium (see, e.g., 44, 45). The general approach is to test extracts of plants used in traditional medicine, determine effects on the uterus, and identify the active ingredient(s) (45–47). There is, however, a lack of a pipeline to take these basic science discoveries forward and bridge the gap to clinical impact on dystocic labors, preterm delivery, or postpartum hemorrhages (PPHs) (48). Cyclotides, which are small, globular, disulfide-rich peptides, have found extensive use in medicinal chemistry due to their stability as organic platforms for therapeutic G protein–coupled receptors research, including development of oxytocin-receptor interactions (49). These extremely useful research tools were discovered in plants from the Violaceae and Rubiaceae (violet and coffee) families. Of note, the latter were studied due to their use in folk medicine to help contractility during labor.

POSTPARTUM HEMORRHAGE

PPH is defined as blood loss ≥500 mL from the genital tract after vaginal delivery of the fetus or ≥1,000 mL after cesarean section. Primary PPH, defined as occurring within the first 24 h after birth, is the most common form of obstetric hemorrhage and cause of obstetric emergency.

Up to 15% of deliveries are complicated by PPH (50), with over 25% of the estimated 300,000 maternal deaths worldwide each year occurring due to PPH (51, 52). The absolute risk of death, however, is significantly greater in low-income countries (1/1,000) compared to high-income countries (1/100,000). Other serious maternal morbidities include multiorgan failure, need for multiple blood transfusions, and hysterectomy. Women at increased risk for PPH include those who have had a prolonged labor, polyhydramnios (excess amniotic fluid), a macrosomic (overly large) fetus, multiple pregnancies, obesity, and pyrexia during labor (53, 54). Less common causes include uterine inversion, extra-genital bleeding, and abnormal placentation such as placenta accreta, where the placenta adheres to the uterine wall, or percreta, where the placenta penetrates through it toward other organs.

The most common cause of PPH is uterine atony, an inability of the uterus to contract adequately after childbirth and delivery of the placenta. During pregnancy, maternal blood volume and cardiac output increase to meet the demand of the developing fetus and placenta. At term,

approximately 20% of cardiac output is directed to the uterus (compared to around 2% in the nongravid). This equates to almost 1 L of blood reaching the uterus every minute (55). Following delivery of the fetus, the placenta must detach from the uterine wall and be delivered, known as the third stage of labor, or afterbirth. The detachment of the placenta from the uterus requires strong myometrial contractions that exert a shear force between the uterine wall and the placenta. At the same time, hemostasis is achieved by compression of the uterine vessels as the uterus contracts to involute. Failure of the uterus to contract following detachment will lead to significant blood loss.

To prevent PPH, the World Health Organization (WHO) (56) recommends active management of the third stage, which can involve early cord clamping, controlled cord traction, and the prophylactic administration of uterotonics before or immediately after delivery of the baby to contract the uterus. When prevention efforts fail and PPH occurs, uterotonics are also given as first-line (i.e., rescue) treatment. There are different uterotonic agents that can be used, but they typically involve ergometrine, oxytocin, or PG analogs or a paired combination such as Syntometrine.

Ergometrine

Ergometrine and methylergometrine are ergot alkaloids with strong uterotonic actions. They are given by intramuscular (IM) or IV injection. Ergometrine injection (0.5 mg) is often administered in combination with synthetic oxytocin (5 units) as Syntometrine, which combines the sustained uterotonic action of ergometrine with the rapid action of oxytocin on the uterus. They are contraindicated in women with hypertensive or cardiovascular disease as they are vasoconstrictive.

Oxytocin and Its Synthetic Analogs Syntocinon and Carbetocin

Oxytocin, or its synthetic analog, Syntocinon, is the most recommended uterotonic for prevention of PPH (56). Compared to no treatment or placebo, oxytocin prophylaxis reduces the risk of PPH (bleeding $\geq$ 500 mL) by approximately 50% (57). Oxytocin can be administered via IV or IM injection. National and international guidelines, for example, WHO, the International Federation of Gynecology and Obstetrics, and the National Institute for Health and Care Excellence, all recommend the use of 10 IU (international units) of oxytocin IM. There is the risk that repeated administration of oxytocin, for example, intrapartum for dystocia, may lead to receptor saturation and desensitization and thereby decrease its uterotonic effect for active management of the third stage.

Carbetocin is another analog of oxytocin but with a longer half-life (~40 min versus 3–5 min) and produces more sustained contractions after a single IV dose (58), negating the need for continuous infusion. Several trials and meta-analyses comparing prophylactic carbetocin with oxytocin have shown a significant reduction in the rates of PPH, use of additional uterotonics, and transfusion in women receiving carbetocin (59–62). Carbetocin is more expensive than conventional synthetic oxytocin, leading to a lack of cost-effectiveness for carbetocin in all patients.

Both oxytocin and carbetocin require refrigeration to maintain potency, which limits their use and distribution in lower-resource settings. A heat-stable formulation of carbetocin (63) has recently been added to the WHO Model List of Essential Medicines (**https://apps.who.int/iris/handle/10665/325771**) and is included in their recommendations on uterotonics for the prevention of excessive bleeding after birth (64). It has since been used in countries where oxytocin is unavailable or its quality cannot be guaranteed.

Prostaglandin Analog

Endogenous PGs are known to increase during labor (65), hence insufficient PGs in the third stage of labor may contribute to uterine atony. In the setting of PPH, PG agents include

carboprost, sulprostone, and misoprostol, which are analogs of $PGF_{2\alpha}$, prostaglandin E_2 (PGE_2), and prostaglandin E_1 (PGE_1), respectively. Carboprost and sulprostone are injectable PGs with IM administration requiring storage at 2–8°C. Misoprostol is water soluble and stable at ambient temperatures. Carboprost is recommended as a second-line uterotonic in PPH treatment, for example, in cases of persistent bleeding after oxytocin treatment, but not for PPH prevention (64). It is superior to other uterotonics in reducing blood loss and shortening the third stage of labor; however, side effects such as vomiting, abdominal pain, and diarrhea are more common (66). These side effects are less severe with sulprostone (67); however, it has been withdrawn in some countries following fears of cardiovascular effects, including cardiac arrest (68).

Misoprostol administration is typically oral but can be given vaginally, rectally, or sublingually, with different respective pharmacokinetic profiles. It is not registered for use in pregnancy but is used off-label with patient consent (66). A number of large RCTs have shown misoprostol (versus placebo) to effectively reduce severe PPH and blood transfusion, and hence misoprostol is considered an effective alternative for managing the third stage of labor (66). More recently, however, a large Cochrane network meta-analysis review (50) found misoprostol to be less effective in preventing PPH ≥1,000 mL when compared with oxytocin.

Combination approaches involving misoprostol or ergometrine with oxytocin for PPH prevention have shown some potential benefits, including reducing the risk of needing additional uterotonics and blood transfusion compared to oxytocin alone (50), but they are associated with increased side effects (vomiting and fever). The addition of misoprostol to oxytocin administration as a first-line treatment, however, is unlikely to add any benefit and is also associated with increased side effects (69).

Other PPH treatments include the anticoagulant tranexamic acid as an adjunct to uterotonic therapy, which has shown reduced death from bleeding in women with PPH (70). Where bleeding cannot be controlled, transfusion of blood with an equal ratio of plasma to blood cells is also recommended (54). Other nonpharmacological management options include uterine massage and balloon tamponade (71).

Future Developments

A key barrier in PPH prevention lies in the availability of and access to good uterotonics, particularly in low- and middle-income countries where most maternal deaths occur. A lack of skilled birth practitioners to administer them is also a factor. Development of new formulations that do not require cold storage and that are noninjectable or orally active will greatly improve access to lifesaving uterotonics across the world. Due to their lack of utero-specificity, however, uterotonics such as oxytocin and carboprost also have unwanted side effects, including hyper/hypotension, arrythmias/tachycardia, and nausea. The possible use of such drugs for abortion has also impacted their development. The development of uterotonics with improved safety profiles and therapeutic windows is warranted.

LABOR PAIN RELIEF

Many women benefit from some form of analgesia in labor. The options available vary widely, with a multitude of pharmacological and nonpharmacological methods at hand. However, one of the most important aspects of discussing analgesia with women is ensuring that their views are heard and respected. In this way, breathing and relaxation strategies, acupuncture, hypnosis, laboring in water, transcutaneous electrical nerve stimulation machines, or massage may be of significant benefit to some women (72). Pharmacological methods of analgesia for labor are principally based upon opioids, inhaled nitrous oxide, and regional analgesia in the form of an epidural.

Opioid analgesia such as diamorphine or pethidine are commonly used for short-term intrapartum analgesia. Pethidine is a synthetic opioid commonly administered via IM injection. In both cases, the action is as an agonist to the μ-opioid receptor, leading to analgesic effects and a wide range of anxiolytic and other side effects.

Entonox is an effective inhalational analgesic consisting of nitrous oxide and air, commonly known as gas and air. It has a long history of use in labor and provides short-lived analgesia but also may cause dizziness, nausea, or vomiting (73). It is rarely used for the entirety of labor but can be useful in the early stages, especially due to the rapid recovery from its effects. Nitrous oxide is an anxiolytic and anesthetic, in addition to being an analgesic. The exact mechanisms of action are still not understood, but its analgesic effects arise in part via opioid receptors (naloxone antagonizes it) in the periaqueductal gray matter. These receptors then stimulate descending noradrenergic pathways acting at α2 adrenoceptors in the dorsal horns. There may also be involvement of other neuromodulators such as γ-aminobutyric acid (GABA) and *N*-methyl-D-aspartate (NMDA) receptors (74, 75).

Epidural analgesia is a form of regional analgesia that relies on the administration of local anesthetic, sometimes with an additional opioid, by a skilled practitioner to the epidural space in the lumbar region of the spine. The goal of epidural analgesia is to provide an effective sensory block that can be titrated to provide long-term analgesic benefit. The use of combined spinal epidural in some labor units is associated with high satisfaction rates and a lower local anesthetic dose.

Nonpharmacological side effects of epidural include an increased length of time for the second stage of labor and an increased chance of instrumental delivery but with no effect on CS rate (76). Additionally, 1% of women will suffer a dural puncture (dural tap), which can cause a significant painful headache.

Future Developments

The main new advances in labor analgesia are around improved mechanisms of epidural administration with computerized, patient-controlled analgesia (PCA) administration. A multicenter PCA RCT of the analgesic remifentanil demonstrated significant reductions in women requiring epidural analgesia and subsequent instrumental delivery (77). Thus, there is the promise of reduced concentrations of local anesthetic or adjuvant therapies and of greater maternal satisfaction with little increased risk.

LABOR INDUCTION

IOL is an increasingly common obstetric intervention and is offered when continuance of a pregnancy would lead to an increased risk to the mother or fetus from remaining in utero and where vaginal delivery is suitable. IOL at or beyond 37 weeks reduces the chances of perinatal death and CS (78). IOL rates have been steadily rising in England from 20.4% of births in 2007–8 to 32.6% in 2017–18 (79), a feature also seen in other countries, with rates of 25.7% in the United States (80) and 34% in Australia (81). The increase in IOL has been led by growing confidence in the safety of induction and its ability to reduce adverse pregnancy outcomes (78, 82, 83). However, despite no direct link with IOL, rates of CS have also been increasing from 19.7% of births in 2000 to 29% in 2018 in the UK (84), a pattern again observed globally (85).

IOL involves a period of cervical ripening, often with a pharmacological agent, followed by rupturing of the amniotic membranes and initiation and maintenance of uterine contractile activity. Nonpharmacological approaches to induction include cervical balloons or osmotic cervical dilators, designed to stretch the cervix to allow amniotomy, with balloons appearing to be

effective (86). Other traditional methods such as membrane sweeping (87) or nipple stimulation (88) to release natural oxytocin have limited evidence of benefit.

The main pharmacological approach to IOL is to use a form of PG for cervical ripening. This process disrupts the collagen fibers of the cervix via an influx of fluid and neutrophils, along with activation of collagenases, which causes progressive weakness of the cervix and an alteration in glycosaminoglycans, with subsequent softening and shortening of the cervix.

Traditionally, cervical ripening is stimulated by the administration of vaginally delivered PGE_2 (dinoprostone) as a gel, tablet, or pessary, with 84% of UK units using vaginal pessary (89). More recently, both vaginal and oral preparations of synthetic PGE_1 (misoprostol), with a similar mechanism of action, have also become available, but uptake has been limited due to concerns about excessive uterine activity (uterine hyperstimulation) (90). The WHO recommends 25 μg oral misoprostol for IOL due to its documented high vaginal delivery and low CS rate (91), with a recent Danish cohort study of 976 women supporting this approach. They found that oral misoprostol is effective and safe in both the inpatient and outpatient setting, with a vaginal delivery rate of 70.1% within 48 h and an overall CS rate of 14.9%, with very few adverse outcomes (92). In addition, this study appears to confirm that the low-dose oral route for misoprostol maintains the effectiveness of vaginal misoprostol at achieving vaginal delivery but minimizes uterine hyperstimulation, a feature observed in other smaller studies (93–95).

Following cervical ripening, a midwife or doctor will often perform an amniotomy (artificial rupture of the membranes), followed by the administration of an IV infusion of oxytocin (Syntocinon). The dose of oxytocin given should be titrated against the frequency of uterine contractions to ensure that there are frequent enough contractions to aid labor progress but not so many as to restrict the reperfusion of the myometrium and placental bed with oxygenated maternal blood or produce subsequent atony.

IOL impacts a woman's birth choices and birth experience, increases need for analgesia, restricts mobility, requires repeated vaginal examinations, and often leads to a longer period in the hospital, both before and during labor (96). Furthermore, for some women, IOL can lead to feelings of loneliness and being undermined and to further concerns about laboring in a strange environment rather than within their birth place of choice (97).

Future Developments

IOL rates show no signs of falling, and as such new developments for effective IOL regimes are urgently required for both clinical efficacy and patient experience. Misoprostol appears to be the most likely candidate to provide new advances for management, especially as newer commercially produced preparations come to market.

PRETERM LABOR

PTB is when a delivery occurs before 37 weeks of pregnancy, which can be either medically induced (iatrogenic) or, in two-thirds of cases, secondary to spontaneous onset of labor. PTB occurs in approximately 15 million pregnancies per year (98) and is responsible for 35% of the world's 2.5 million newborn deaths (99). Even in those children who survive, there are significant risks of physical, neurological, and behavioral morbidity as a consequence of being born preterm (100).

Pharmacological approaches are used both to prevent PTB in high-risk women and to treat women in threatened preterm labor to prevent delivery and improve the situation for surviving children. Nonpharmacological treatments to prevent PTB include cervical cerclage (i.e., a stitch to close the cervix), cervical pessary, fish oil supplementation, zinc, and bed rest (100).

Pharmacological Prevention of Preterm Birth

Progesterone has been advocated for the prevention of PTB by promoting thickened cervical mucus and uterine quiescence, although the exact mechanism of action remains elusive. Progesterone can be administered either as a natural vaginal pessary or as an IM injection of synthetic 17-α hydroxyprogesterone caproate (17-OHPC) (101).

There has been conflicting evidence for the benefits of progesterone to prevent PTB in women at high risk. Typically, women at high risk would have a history of a previous PTB or prelabor preterm rupture of the membranes (PPROM), often in addition to evidence of shortened cervical length (102). Confusion has existed for many years over the varying inclusion criteria of the different studies of PTB intervention and the type of progesterone administration, be it vaginal or IM (17-OHPC).

For vaginal progesterone, large studies have shown both benefit (103–105) and no benefit (106, 107) in reducing PTB in high-risk populations. Despite the lack of clear evidence of benefit, some guidance has advocated for the use of vaginal progesterone due to the significant harm and financial cost from failure to prevent PTB (108). The story is similar to that of IM 17-OHPC, with some studies showing beneficial effects on preventing PTB (105) while others show no advantage (109, 110).

A recent, very large meta-analysis of individual participant data from RCTs of all progesterone usage for PTB prevention has resolved the uncertainty by confirming that both vaginal progesterone and 17-OHPC have a significant role in preventing early delivery in women with a singleton pregnancy who are at high risk of PTB, and especially so in those with a short cervical length (111).

Treatment of Preterm Birth

Tocolysis is the use of drugs in an attempt to delay the delivery of the baby when the birth will be preterm. These drugs are referred to as tocolytics, and many different types have been used for many years to prevent uterine contractions.

Betamimetics (such as terbutaline or ritodrine) activate adenyl cyclase to increase intracellular cyclic adenosine 3′,5′ monophosphate (cAMP). This rise in cAMP reduces myosin light-chain kinase activity and prevents contraction of the myometrial smooth muscle. Betamimetics reduce the number of women giving birth within 48 h when compared to placebo (112). However, they do not appear to reduce overall PTB rates or perinatal death. In addition, the use of betamimetics in many countries is limited due to their association with a range of potentially serious maternal and fetal side effects (113).

Oxytocin receptor antagonists such as atosiban competitively inhibit the binding of the peptide hormone oxytocin to the oxytocin receptor on the myometrial smooth muscle cell. This prevents the oxytocin-mediated influx of intracellular calcium, which is responsible for myometrial contraction. Oxytocin receptor antagonists are not effective tocolytics in that they do not prevent PTB within 48 h or perinatal morbidity or mortality (114). However, they do have a better safety profile than either betamimetics or calcium channel blockers.

Calcium channel blockers such as nifedipine prevent the influx of extracellular calcium into the smooth muscle cells of the myometrium, thereby preventing uterine contractions. Calcium channel blockers appear to be moderately effective at preventing PTB within 48 h and have fewer side effects than betamimetics (115).

PGs are a family of metabolites of arachidonic acid produced by cyclooxygenases (COXs). They have strong uterotonic properties, with $PGF_{2\alpha}$ and PGE_2 being the best studied in the myometrium in labor. Inhibitors of COX such as indomethacin prevent the normal production of

prostaglandins. Given their role in the initiation of labor, the inhibition of prostaglandin production is proposed to maintain uterine quiescence. COX inhibitors may be slightly better at preventing PTB than other tocolytics, though the data are limited, and may also have a better safety profile (116). However, concern remains over the risk of placental transfer causing premature closure of the fetal ductus arteriosus.

The Cochrane library suggests that there is inadequate evidence to support the use of magnesium sulfate (117) or nitric oxide donors (such as glyceryl trinitrate) (118) to prevent PTB.

Unfortunately, all tocolytics found to date have only limited effectiveness, and several have potentially serious side effects for the mother or fetus. This has led UK national guidelines to suggest only limited use of tocolytics to allow transfer of an at-risk mother and fetus to a unit with more appropriate neonatal facilities or in order to allow time for antenatal corticosteroids (108).

Future Developments

Basic science, including pharmacological, physiological, and transcriptomic studies, has already shed light on potential druggable targets for therapeutic regulation of uterine contraction, for example, the oxytocin receptor (OTR), and has identified some causes of preterm labor (113). A significant problem with current tocolytic offerings, however, is the effect on the fetus. Coadministration of multiple treatments at lower doses may offer a safer and more effective solution, particularly where the combination targets different cellular pathways. Recently, an orally active, selective prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) receptor antagonist, ebopiprant (OBE022), has been developed as a potential treatment of preterm labor, having both tocolytic and anti-inflammatory actions. In a Phase IIa proof-of-concept, randomized, double-blind, placebo-controlled trial (PROLONG), ebopiprant reduced the number of women delivering preterm in 48 h by 55% compared to atosiban alone.

Development of novel tocolytics that significantly delay preterm labor or prevent it will arise from furthering our understanding of the mechanisms that drive myometrial contraction and spontaneous preterm labor onset, which may also include exploring differences in women experiencing preterm labor to develop a personalized medicine approach to treatment. Additionally, reformulation of existing drugs using nanotechnology to improve methods of their delivery, for example, uterine-targeted strategies using liposomes, is a promising alternate approach to increasing efficacy and safety (119, 120).

OPTIMIZATION OF NEONATAL CONDITION IN PRETERM BIRTH

Magnesium has been used extensively in obstetrics to treat eclampsia in mothers. From these beginnings it was recognized that neurological outcomes such as cerebral palsy and intraventricular hemorrhage may be improved in babies whose mothers had received magnesium. In women at risk of PTB, administration of magnesium sulfate prior to birth provides neonatal neuroprotection and reduces the risk of cerebral palsy and gross motor dysfunction but without an effect on mortality (121). Overall, 63 women would need to be treated to avoid one case of cerebral palsy.

Measures to reduce respiratory distress syndrome (RDS) in the neonate involve the use of antenatal corticosteroids (dexamethasone or betamethasone) administered to the mother in the 24 h before delivery. Use of corticosteroids reduces perinatal and neonatal mortality and RDS and may possibly reduce intraventricular hemorrhage and neurodevelopmental delay (122).

Antibiotics have been advocated to prevent PTB but have no consistent evidence of benefit in women with intact membranes (123, 124). In women with PPROM, use of the macrolide antibiotic erythromycin reduced neonatal harm and prolonged pregnancy compared to co-amoxiclav (125). There remains the risk of harm to the child up to 7 years after administration of erythromycin

or co-amoxiclav (126), but educational attainment is not substantially different at 11 years of age (127).

CONCLUSIONS

Pharmacological approaches to the management of a small number of important obstetric complications are critical to the successful management of these conditions. They are employed in pregnancies deemed to be high risk, such as PTB prevention, but are also critical in otherwise normal pregnancies that stray into the realm of pathology, such as threatened PTB, labor induction, management of labor dystocia, and PPH. As such, pharmacological approaches to obstetric care are an essential part of the modern obstetrician's armory and can be required in any pregnancy no matter how low risk it is initially classified as being.

There are few choices of drugs for some conditions, for example, dystocia, and this therefore remains a major contributor to unplanned CS rates. There are a range of drugs for PTB prevention, but none are delivering consistent effects, and the incidence of preterm delivery is little changed in the last decade. In the developed world, significant harm from PPH is uncommon due to prophylactic and rescue administration of uterotonic drugs. Unfortunately, in the developing world, obstetric hemorrhage is a leading cause of maternal death. Future developments that will improve the pharmaceutical armory in obstetrics have been highlighted, but more research, innovation, and clinical trials are urgently needed.

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