Prostaglandins for Postpartum Hemorrhage: Pharmacology, Application, and Current Opinion

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Keywords

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Abstract

Background: Postpartum hemorrhage (PPH) remains a common cause of maternal mortality worldwide. Medical intervention plays an important role in the prevention and treatment of PPH. Prostaglandins (PGs) are currently recommended as second-line uterotonics, which are applied in cases of persistent bleeding despite oxytocin treatment. **Summary:** PG agents that are constantly used in clinical practice include carboprost, sulprostone, and misoprostol, representing the analogs of PGF_{2α}, PGE₂, and PGE₁, respectively. Injectable PGs, when used to treat PPH, are effective in reducing blood loss but probably induce cardiovascular or respiratory side effects. Misoprostol is characterized by oral administration, low cost, stability in storage, broad availability, and minimal side effects. It remains a treatment option for uterine atony in low-resource settings, but its effectiveness as a uterotonic for independent application may be limited. **Key Messages:** The present review article discusses the physiological roles of various natural PGs, evaluates the ex-

isting evidence of PG analogs in the prevention and treatment of PPH, and finally provides a reference to assist obstetricians in selecting appropriate uterotonics.

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Introduction

Postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality. It accounts for approximately 25% of all deaths of pregnant women worldwide, with an estimated 127,000 deaths per year [1–4]. PPH has an overall incidence of about 6% and is associated with serious morbidity. Occasionally, blood transfusions are required with this condition. Moreover, PPH may lead to renal failure, coagulation deficiencies, anemia, and surgical procedures that can result in loss of fertility. Epidemiologic studies have indicated that the incidence of PPH has been steadily increasing even in many well-resourced countries, for unknown reasons [5]. Between 1994 and 2014, rates of PPH have increased by 26%, and there has been a 50% rise in PPH caused by uterine atony [6, 7].

Fig. 1. Metabolism of arachidonic acid. Membrane-bound PG receptors are shown in blue boxes. Cyclooxygenase and related enzymes are shown in red. PG, prostaglandin.

PPH is usually defined as a blood loss >500 mL following a vaginal birth or a loss of >1,000 mL after a cesarean birth [8]. The increased rates of atonic PPH have emphasized the importance of active management in the third stage of labor [9]. Data from several large randomized trials have demonstrated that the prevalence rate of PPH of >500 mL was approximately 5% when active management was applied compared with 13% when expectant management was used [10]. The evidence appeared to show that active management reduced the average risk of severe primary PPH (>1,000 mL) at birth. Therefore, it is essential to perform close monitoring, implement additional measures as necessary, and check for the cause of bleeding, especially for women with possible high-risk factors. One such measure is the admin-

istration of uterotonics, which is routinely performed postdelivery to prevent excessive postpartum bleeding due to uterine atony [11].

Traditionally, oxytocin has been the treatment of choice for the prevention and treatment of PPH. Compared to no uterotonics [12, 13], oxytocin prophylaxis is associated with a reduced risk of PPH, but refractory uterine atony can occur when the uterus fails to adequately contract after oxytocin administration. Owing to the saturation of oxytocin receptors, oxytocin confers the disadvantage of receptor desensitization with repeated injections. In addition, it requires refrigerated conditions for storage and professional personnel for its administration, making it difficult to access in remote, low-resource settings. In the setting of refractory uterine atony, approxi-

mately 3–25% of patients require other uterotonics to promote uterine contraction after oxytocin injection [8].

Prostaglandin (PG) agents, as second-line uterotonics, are widely used in contemporary obstetric practice [14]. PGs have strong uterotonic properties, and such agents may be used within obstetrics and gynecology for the purpose of cervical ripening, termination of pregnancy, induction of labor, and PPH [15, 16]. In the process of labor, maternal concentrations of endogenous PGs increase gradually in the first stage and steeply in the second stage, and then peak immediately after delivery of the placenta. Noort et al. [17] showed the concentrations of plasma prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) metabolite at placental separation were markedly higher than those at full cervical dilatation, and the concentrations were highest 5 min after placental separation. Their study showed that one of the possible reasons for uterine atony could be insufficient increase in PG concentration in the third stage of labor. Furthermore, according to the same study, PGs also stimulate the production of oxytocin receptors [18]. Therefore, the application of PGs for the prevention and management of PPH was a logical extension of their critical pharmacological effects in labor. The properties of PGs leading to sustained myometrial contractility are well suited to the management of PPH and its complications.

Pharmacological Role of PGs in the Uterus

PGs are a series of metabolites formed from arachidonic acid, which are mainly produced by cyclooxygenase (shown in Fig. 1). PGs were originally thought to activate membrane receptors near their formation site. Their different biological activities and generation of second messengers (cyclic AMP [cAMP], inositol phosphates, and Ca^{2+} [IP3/ Ca^{2+}]) suggested that PGs interact with distinct receptors, and different receptors correspond with different PGs [19]. It was determined that prostaglandin D_2 (PGD_2), prostaglandin E_2 (PGE_2), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), prostacyclin I_2 (PGI_2), and thromboxane A_2 (TXA_2) exert their biological function by interactions with their respective receptors – the DP, EP, FP, IP, and TP receptors [20]. Four subtypes of EP receptor have been identified (EP_1 – EP_4) (Fig. 1). PG receptors are located in the myometrium, trophoblast cells, amnion, and cervix, and all belong to the G-protein-coupled superfamily, incorporating 7 transmembrane domains [21].

The PGs produced in the human endometrium are mainly those of the E and F series, while PGD_2 , PGI_2 , and TXA_2 occur less frequently [22]. $PGF_{2\alpha}$ action is mediated

by the FP receptor, increasing the intracellular calcium concentration ($[Ca^{2+}]_i$) via the PLC-IP₃- Ca^{2+} pathway. PGE_2 acts differently through 4 subtypes (EP_1 – EP_4) in human myometrium: its interaction with EP_1 receptors elevates $[Ca^{2+}]_i$ via the PLC-IP₃- Ca^{2+} pathway, while EP_2 and EP_4 receptor signals stimulate the production of adenylyl cyclase. Overall, differences in biological functions of the PG receptors reveal 3 subclusters (shown in Fig. 2). The first of these subclusters consists of receptors TP, FP, and EP_1 , which increase $[Ca^{2+}]_i$ and constitute a group of “contractile” receptors because they cause smooth muscle contraction. The second group consists of receptors IP, DP, EP_2 , and EP_4 , which increase the concentration of intracellular cAMP via Gs protein and are defined as “relaxant” receptors because they induce smooth muscle relaxation. Finally, the third group consists only of EP_3 and is generally associated with a decline in cAMP. The “inhibitory” receptor generally causes smooth muscle contraction, depending on the cell type; however, the EP_3 receptor can also increase intracellular cAMP and induce $[Ca^{2+}]_i$ [23].

PGs in Pregnancy and Birth

Interestingly, the nonpregnant human uterus contracts in the presence of $PGF_{2\alpha}$ and TXA_2 but relaxes in the presence of PGE_2 [24]. Uterine strips isolated from pregnant women contract with $PGF_{2\alpha}$ and low concentrations of PGE_2 , while PGI_2 and high concentrations of PGE_2 induce relaxation [24]. One possible explanation for this is that PG receptor expression varies considerably from the nonpregnant state through pregnancy to birth, and the relative level or type of receptors may dictate the degree of uterine quiescence or contractility [25]. For example, the uterine FP mRNA expression level has been found to decline significantly with gestational age in patients not in labor and then at term increase significantly with labor [26]. Thus, in the initiation of parturition, myometrial active quiescence may change to an active contractile state due to an upregulation of contractile receptors and downregulation of relaxatory receptors [27, 28]. Moreover, the additional control for the onset of labor is built into the increased synthesis of endogenous PGs of the E and F series in the uterine compartment [29, 30]. The intra-amniotic, intravenous, or vaginal administration of exogenous PGs can initiate labor at any stage of gestation and in all mammalian species. For pregnant women in labor and placental delivery, PGE or $PGF_{2\alpha}$ produces a dose-dependent increase in the frequency and

Fig. 2. Prostanoid receptors and their primary signaling pathways. Prostanoid receptors are members of the G-protein-coupled receptor superfamily. The terms "relaxant," "contractile," and "inhibitory" refer to the phylogenetic characterization of their primary effects.

intensity of uterine contractions [24]. Additionally, PGE₂ appears to play a more important role in cervical ripening and rupture of the fetal membranes than in uterine contractility [31].

However, natural PGs may be associated with rapid metabolism, unstable chemical properties, and a number of adverse reactions that limit their clinical applications. Numerous PG analogs have therefore been developed for appropriate clinical use. The preparations are available in the form of injections, tablets, or suppositories based on their intended application. The objective of this review was to evaluate the existing evidence on the roles of various PG analogs in preventing and treating PPH and to consider their differences in adverse reactions in clinical use.

PG Analogs for PPH

In the prevention and treatment of PPH, the PG agents that are frequently used in clinical practice include carboprost, sulprostone, and misoprostol, representing the analogs of PGF_{2α}, PGE₂, and PGE₁, respectively [32].

Side Effects

Smooth Muscle

Endogenous and synthetic PGs also contract or relax smooth muscles in tissues outside the uterus. In general, TXA₂, PGF_{2α}, and PGD₂ contract, while PGE₂ and PGI₂

relax the bronchial and tracheal smooth muscles. Numerous case reports have been documented of life-threatening bronchospasm associated with carboprost (a synthetic PGF_{2α} analog) [33]. PGEs and PGFs also induce contraction of the main longitudinal muscle in the gastrointestinal tract and increase the movement of water as well as electrolytes into the intestinal lumen. Such physiological effects could explain the watery diarrhea that follows oral or parenteral administration. Generally, diarrhea, cramps, and reflux of bile have been caused by PG agents as well as endogenous PG release such as labor (nausea and hyperthermia), which are common side effects in patients administered PG analogs (including carboprost, sulprostone, and misoprostol) for clinical use.

Cardiovascular System

Generally, PGs do not directly affect systemic vascular performance. They may, however, modulate local vascular tone at the site of their formation and ultimately affect systemic blood pressure [34]. In most blood vessels, PGE₂ elicits vasodilation and a slight drop in blood pressure. PGF_{2α} is a potent constrictor of both pulmonary arteries and veins. Blood pressure is increased by PGF_{2α} in humans. However, the observed influence of PG analogs on blood pressure is clinically insignificant, although carboprost should be used with caution in hypertensive patients. Direct inotropic effects have been noted with sulprostone (a synthetic PGE₂ analog) [35, 36], especially

when administered directly into the uterine wall. However, there is a contradiction between the role of sulprostone as a coronary artery dilator and the coronary vaso-spastic hypothesis that causes serious cardiovascular side effects related to sulprostone. Experimental studies [37, 38] analyzed the role of endogenous PGE₂ in regulating coronary artery resistance and pointed out its vasodilatory effect on arterioles and inhibition of endothelium-myeloid cell interactions; especially in the presence of ischemic factors, it can limit the infarct size. It is considered the treatment with some clinically available PGE analogs, such as misoprostol, could reduce the injury of ischemic cardiomyopathy [38]. Furthermore, we noticed the cases of severe cardiovascular or respiratory side effects reported with the use of injectable PGs to control atonic PPH were associated with the route of administration that is not recommended, high combined doses of both sulprostone and carboprost, or hemorrhagic shock [39–41]. Therefore, in terms of drug labels and clinical management guidelines [42], direct intramyometrial injections are not approved for sulprostone.

CNS

The fever caused by a variety of endogenous and exogenous pyrogens is mediated by PGE₂ [24]. PGE₂ crosses the blood-brain barrier and acts on EP₃ or EP₁ in thermosensitive neurons. This stimulates the hypothalamus to elevate the body temperature by promoting increased heat production and reduced heat loss. PGF_{2α} induces fever but does not participate in the pyretic response. The PG analogs in clinical applications, especially misoprostol, have been shown to be associated with a significantly higher rate of shivering and a body temperature >38°C [43]. A large multicenter study [44] reported an unusually high rate of fever >40°C (36%) in Ecuadorian women who received 800 µg of misoprostol sublingually compared with other participants (0–9%) who received the same regimen. Since the incidence of fever varies greatly in different populations, there is hypothesis that genetic factors may play a role in misoprostol-induced fever [45]. Some studies [46] suggest that genetic variability in ABCC4 and the resultant higher level of misoprostol acid in the brain lead to hyperpyrexia in pregnant women. But after treatments, such effects were related, transient, self-limiting, and do not result in additional health complications [47].

Eye

Prior to the 1970s, studies had demonstrated that the effect of PGF_{2α} on the eye was to elevate intraocular pres-

sure. Consequently, glaucoma has been a contraindication to the administration of PGF_{2α} analogs. Until 1977, studies [48] had confirmed that PGF_{2α}-induced constriction of the iris sphincter muscle and its overall role on the eyes was to reduce intraocular pressure by increasing the outflow of aqueous humor. This represented a dramatic reversal, in our understanding, of the role of PGs in relation to the eye. Since then, a range of FP receptor agonists have proved effective in the treatment of glaucoma [49]. However, in China, the domestic instructions pertaining to PGF_{2α} agents have not been updated in regard to glaucoma as a contraindication. Pharmaceutical companies and national drug administrations have now been informed about the contraindication on the use of PGF_{2α} agents in this context.

Injectable PGs

Injectable PG analogs such as sulprostone and carboprost are generally regarded as second-line uterotonics in PPH treatment. They induce strong and sustained myometrial contractions and have a reported efficacy of 87–92% [50]. Injectable PGs are unequivocally considered as suitable medications for PPH treatment, but not for its prevention. For women at low risk of PPH, injectable PGs are related to more frequent cardiovascular or respiratory side effects [51]. In addition, injectable PGs are currently not available in all medical facilities, and where they are available, the drug cost is high [46]. Therefore, in many clinical management guidelines, injectable PGs are not recommended for the prevention of PPH [52–54]; only if oxytocin or other first-line uterotonics do not provide adequate uterine tone, injectable PGs should be considered. Administration of injectable PGs should be guided by the clinical context and presence of contraindications and follow local hospital policies and availability.

Carboprost

Carboprost is an analog of PGF_{2α}. The rapid metabolism of natural PGs limits their clinical application and promotes the development of analogs with longer durations of action. Carboprost tromethamine is a mixture of 15-methyl PGF_{2α} and tromethamine (shown in Fig. 3). The oxidation of carboprost, with the hydrogen being replaced by a methyl group, is completely restricted [55]. It has the same pharmacological action as PGF_{2α}, the contraction intensity of the uterus being 20–100 times stronger than that of PGF_{2α}. In clinical practice, 80% of patients with uterine atony exhibited a response below 250 µg, and 95% of patients showed a response below 500 µg [56]. Dildy's statistics on 1,237 cases of carboprost application

Fig. 3. Structural formula of PGF_{2α} and carboprost. PG, prostaglandin.

in 12 medical institutions showed that the effective percentage was 94.19% [57].

In cases of continuous bleeding that is refractory to the administration of oxytocin or ergot alkaloids, injectable PGs are considered the second therapeutic step. Compared to conventional uterotonics, carboprost results in less blood loss and shorter duration of the third stage of labor, but vomiting, abdominal pain, and diarrhea were more common with carboprost administration [15].

Carboprost can, however, cause bronchospasm. Increases in pulmonary and systemic vascular resistance together with intrapulmonary shunting can trigger desaturation of arterial hemoglobin oxygen. Asthma patients are particularly susceptible to these complications, but there are some reported cases of bronchospasm in patients without asthma [58]. It is worth noting that PGF_{2α} is an endogenous compound involved both in physiology and in pathology. Many preclinical and clinical studies [59] have revealed PGF_{2α} to be associated with severe acute or chronic inflammatory diseases such as rheumatic diseases and is a risk factor for atherosclerosis, diabetes, ischemia-reperfusion, septic shock, and many other conditions. For patients with the above diseases, carboprost should be used with caution, especially when repeated injections are necessary.

Sulprostone

The Dutch, German, and French guidelines [42, 60, 61] recommend the application of sulprostone, a PGE₂ analog, in cases of persistent bleeding despite oxytocin treatment. It is usually administered by intravenous infusion; intramuscular and intramyometrial injections are contraindicated for sulprostone. A comparative study on the clinical use of sulprostone and carboprost revealed significantly fewer side effects for sulprostone [62]. However, as case reports [35, 36] found it to be associated with cardiac arrest in 3 women, manufacturers – with the exception of certain

European countries – later withdrew the drug. While obstetricians may be reluctant to use sulprostone on account of its reported side effects, this issue is controversial because no causal relationship has been documented and the actual frequency of these events remains unknown.

The current French guidelines recommend the use of a continuous intravenous infusion of sulprostone within 30 min after PPH diagnosis if bleeding persists after oxytocin administration, and also that the dose should not exceed 500 µg in the first hour and 1,500 µg in total. In some population-based studies, with close medication monitoring, sulprostone is thought to be a safe and effective choice for patients with placental retention [63] or for patients with PPH. Severe cardiovascular or respiratory side effects have been found to be uncommon (i.e., a prevalence of 0.1–1% according to the World Health Organization) [64].

Misoprostol

Misoprostol, a PGE₁ analog registered for the prevention and treatment of peptic ulcer and upper gastrointestinal hemorrhage caused by nonsteroidal anti-inflammatory drugs, has attracted widespread attention because of its strong uterotonic effects and ease of administration. El-Refaey [65] reported the first use of oral misoprostol for the management of the third stage of labor in an observational study. Compared with naturally occurring PGE₁, misoprostol exhibits superiority in many aspects. It transforms the chemical structure of natural PGE₁ into a more stable form. These modifications (shown in Fig. 4) increase oral activity, duration of action, and safety [66].

Misoprostol is not registered for use during pregnancy, but in most countries, physicians may conduct off-label drug use with appropriate informed patient consent [67]. The clinical applications of misoprostol in gynecology and obstetrics include medically induced abortion, induction of labor, cervical ripening, and treatment of

Fig. 4. Structural formula of PGE₁ and misoprostol. PG, prostaglandin.

Table 1. Pharmacokinetic parameters of oral, vaginal, sublingual, and rectal misoprostol

	Oral	Vaginal	Sublingual	Rectal	References
Time to peak, min	14.2±7.0	65.0±21.2		71.7±23.5	[71]
	27.5±14.8	72.0±34.5	26.0±11.5		[72]
Peak level, pg/mL	258.7±83.8	210.8±63.0		86.8±44.7	[71]
	287.6±144.3	125.2±53.8	574.8±250.7		[72]
Area under the curve to 240 min, pg·h/mL	151.8±61.1	446.0±172.1		188.9±126.1	[71]
	369.3±155.2	329.7±139.0	702.1±274.8		[72]

Values are expressed as mean ± SD.

uterine atony. The oral preparation offers stability at room temperature and is significantly cheaper than PGE₂ and other analogs. Although misoprostol is administered orally, there are also vaginal, sublingual, buccal, and rectal routes. Rectal administration has been used for the prevention and treatment of PPH [68]. Pharmacokinetic evaluations of misoprostol absorption when administered by various routes have been performed [69–72]. In these studies (shown in Table 1), following an administration dose of 400 µg, misoprostol demonstrates a route-dependent pharmacokinetic profile.

In terms of drug peak time, the oral and sublingual administrations seem to be superior. Sublingual misoprostol achieved the highest peak plasma concentrations ($C_{\max}$) (574 ± 250.7 pg/mL), and this was significantly higher than those in oral and vaginal routes, which was 287.6 ± 144.3 and 125.2 ± 53.8 pg/mL, respectively. The time to peak concentration ($T_{\max}$) was similar in both the sublingual (26.0 ± 11.5 min) and oral routes (27.5 ± 14.8 min), which was significantly shorter than those in the vaginal route [72]. Vaginal administrations of misoprostol show a slower pattern and a longer time ($T_{\max}$ = 72.0 ± 34.5 min) to peak plasma concentrations ($C_{\max}$ = 125.2 ± 53.8 pg/mL) [72], but the reduction in plasma concentration is also much slower, with corresponding advances

in bioavailability generally. In another pharmacokinetic study of misoprostol [71], the bioavailability of vaginal route as shown by $AUC_{[240]}$ was 446.0 ± 172.1 (pg·h/mL), greater than either oral or rectal misoprostol. In addition, rectally administered misoprostol is similar in terms of its absorption curve to that of vaginal misoprostol, but is lower in bioavailability, which was expressed by $AUC_{[240]}$ (188.9 ± 126.1 pg h/mL) [71]. The change in plasma concentrations corresponds to the effect on uterine contractility. Taken together, it is considered that the period from the start of treatment to an obvious effect is notably shorter following sublingual and oral administration, and the duration of effect is significantly longer by vaginal and rectal administration. These conclusions will help optimize existing regimens and identify the ideal routes of administration for different clinical indications. In the treatment of PPH, prompt myometrial contractility should be induced by misoprostol, according to pharmacokinetic studies, and oral or sublingual route is preferred with the shortest interval to peak concentrations. In many clinical management guidelines, a single oral/sublingual/rectal dosage of 600–1,000 µg is advocated on PPH in uterine atony (shown in Table 2). Furthermore, a variety of doses and routes of administration [73–75] have been tested using control regimens that have included

Table 2. Recommendations on the use of misoprostol in the management of PPH

	Dose and route	Continuing dose	Precautions/contraindications	Adverse effects
ACOG (2017)	600–1,000 µg sublingual, oral, or rectal	n.e.	Rare, hypersensitivity to medication or to PGs	Nausea, vomiting, diarrhea, shivering, fever (transient), and headache
RCOG (2016)	800 µg sublingual	n.e.	Not mentioned	Not mentioned
FIGO (2012)	800 µg sublingual	n.e.	Second-line treatment if oxytocin is not available or failed	Risk of pyrexia
SOGC (2018)	400–800 µg oral, sublingual or 800–1,000 µg rectal	n.e.	Off-label use. Duration of effects is longer for rectal route	Higher rate of pyrexia for oral route
Queensland (2020)	800–1,000 µg sublingual or per rectum	n.e.	Use when oxytocin and ergometrine are not successful. Due to slow onset of action, consider early administration	Increases pyrexia >38°C, >40°C reported in 1–14%

PG, prostaglandin; PPH, postpartum hemorrhage.

ed conventional and nonconventional uterotonic, as well as placebo. It is considered that 400–600 µg misoprostol administered orally is optimal for PPH prevention and 800 µg sublingual misoprostol has the most evidence supporting its safety and efficacy for PPH treatment [76, 77]. It is worth noting that rectal administration has also been proposed for application in the third stage of labor. There may be 2 reasons for this application. First, rectal misoprostol likely has a higher degree of bioavailability because the rectal mucosa is moister in the third stage of labor and thus enhances absorption. Second, there are advantages in considering combined dosage regimens that utilize the absorption speed of oral administration, as well as the higher level of bioavailability, and the longer duration of effect, regarding the rectal route in the third stage of labor and postpartum. Vaginal administration may not be practical in active PPH with massive vaginal bleeding.

As a second-line agent for the prevention and treatment of uterine atony, misoprostol has been suggested as an alternative for the routine management of the third stage of labor. In a meta-analysis [15] of numerous large RCTs comparing misoprostol versus placebo administration, oral or sublingual misoprostol has been shown to be effective in reducing severe PPH and blood transfusion. Compared with conventional injectable uterotonics, oral misoprostol was associated with higher risk of severe PPH, but with a trend toward fewer blood transfusions. Another network meta-analysis [78] comprising 140 randomized trials with data from 88,947 postpartum women indicated the 3 most effective drugs for the prevention of PPH ≥500 mL were ergometrine plus oxytocin, carbeto-cin, and misoprostol plus oxytocin combined. It has been suggested that misoprostol, as an adjuvant to oxytocin,

can also be applied for earlier interventions when uterine atony is refractory. Overall, when considering areas with poor medical services, the supply and storage of expensive or light-sensitive or temperature-sensitive medications are limited, and misoprostol offers an uterotonic alternative that is inexpensive and easy to store [79]. In 2011, the WHO added misoprostol for the prevention of PPH to the Model List of Essential Medicines, thus solidifying recommendations for its use, including dose and route of administration.

Misoprostol appears to have no serious side effects, in appropriate doses and durations, for the treatment of uterine atony. However, it is associated with higher rates of shivering and fever, along with other PG-related side effects such as nausea, vomiting, and diarrhea. Following misoprostol administration, few women have been shown to have a body temperature >40°C during the first hour after delivery. For every 7–9 women given 600 µg of misoprostol, 1 additional woman will have “shivering”; for every 17–21 women, 1 additional woman will have a body temperature >38°C [43]. Taken together, the incidence of fever for misoprostol reportedly varies from 10 up to 50% [44, 80, 81], which is related to both its dosage and route with the highest incidences found in the high-dose sublingual routes, owing to its pharmacokinetics [82]. However, this is not the only influence on postnatal fever. There appear also to be other effects that could be genetic or cultural [44, 45]. Clinically, it is worth noting that fever as the side effect of misoprostol and fever caused by postpartum infection need to be distinguished more carefully [83]. There are no contraindications to using misoprostol in postpartum women except in those with a history of an allergic reaction. Asthma is not a contraindica-

tion as misoprostol is a weak bronchodilator. These tablets do not cause hypertension, which enables them to be used for hypertensive patients.

Conclusion

Both injectable PGs and misoprostol are preferable as part of the management in the third stage of labor when the first-line treatments for uterine atony have proved ineffective. The choice of which medication to apply should be based on the patients' specific details and the clinical diagnosis of the obstetrician in charge of the case. Therefore, it is important for practitioners to understand both the risks and benefits of commonly used PG agents. Optimizing their use might help mitigate progression to severe PPH and reduce the need for invasive procedures. As side effects are dose related, optimal effective dose and route of administration during PPH remain an area of active research. We look forward to further advances in preventing and treating PPH in the future.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

Y.C. drafted the manuscript. C.H.Z. carried out conceptualization. W.J. assisted in reviewing literature. Y.C. designed and drew the figures in the manuscript. The manuscript was modified by Y.C.Z. and D.L.S. F.W. and X.Z. helped in reviewing the first draft of the manuscript. All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

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