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The preventive effect of prostaglandins on postpartum haemorrhage after normal deliveries and caesarean sections

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Abstract

Purpose: To «count» the prophylactic effect of prostaglandins administration (misoprostol with or without the co-administration of prostaglandin F2a) in the postpartum haemorrhage after normal delivery and after cesarean section.

Material-Methods: The study took place in Athens, Greece during the period 1990-2018. The cases included in the study were divided into 2 groups. No prophylactic uterotonic agent was administered in the patients of the first group which included 335 normal deliveries and 205 cesarean sections. On the contrary, prophylactic administration of misoprostol and, if necessary, the additional administration of prostaglandin F2a was performed in all patients of the second group which included 498 normal deliveries and 377 cesarean sections.

Results: The prophylactic administration of prostaglandins resulted in the prevention of postpartum haemorrhage with no need for blood transfusion or invasive procedures.

Conclusion: The prophylactic administration of prostaglandins results in the prevention of postpartum haemorrhage after both normal deliveries and cesarean sections.

Introduction

Postpartum haemorrhage (PPH) is defined as the loss of more than 500 ml of blood after vaginal delivery and more than 1000 ml after caesarean section (CS). Most occur within 24 hours following labour and are called early PPH. Late PPH is defined as excessive bleeding occurring between 24 hours after delivery and 6 weeks postpartum. Blood loss occurs in 4% of vaginal deliveries and 6% of caesarean deliveries. Two percent of cases are presented with severe bleeding [1]. A decline in haematocrit of 10 points has been proposed as a definition of PPH [2].

Blood flow to the gravid uterus at term is 800 to 1000 ml/min and large amounts of blood can be lost rapidly [3]. Without mechanisms to minimize blood loss, maternal exsanguination could occur rapidly. The uterus contracts after delivery of the placenta and this contraction (rather than formation of clots or aggregation of platelets) is the major mechanism for haemostasis after delivery. Strategies to treat early PPH first must ensure uterine contraction and then identify and repair possible genital tract injuries, retained placenta/membranes and coagulation failure. Fifty percent of early PPH cases are due to uterine atony [4]. If the uterus is contracted, the leading causes of early PPH include genital tract trauma and pathologic placentation.

500.000 maternal deaths occur worldwide every year. Up to 50% of these can be attributed to obstetric haemorrhage. As a result, obstetric haemorrhage is associated with significant mortality [5] and is the third leading cause of direct maternal death [6]. Risk factors and causes of PPH are included in Tables 1 and 2 respectively.

Table 1. Risk factors for postpartum haemorrhage [7]

Prior postpartum haemorrhage
Advanced maternal age
Multifetal gestation
Prolonged labour
Polyhydramnios
Instrumental delivery
Fetal demise
Placental abruption
Anticoagulation therapy
Multiparity
Fibroids
Prolonged use of oxytocine
Macrosomia
Caesarean delivery
Placenta praevia and placenta accreta
Chorioamnionitis
General anaesthesia

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Table 2. Causes of postpartum haemorrhage [7]

Early causes
Uterine atony (50% of cases)
Genital tract lacerations (20% of cases)
Retained products (5-10% of cases)
Abnormal placentation
Coagulopathies and anticoagulation
Uterine inversion
Amniotic fluid embolism
Late causes
Retained products
Uterine infection
Subinvolution
Anticoagulation

The most important aspect of PPH management and treatment is prediction and prevention. A detailed medical history is necessary to determine the risk factors for PPH (Table 1). Immediately following placenta delivery, uterotonic agents should be administered in order to prevent uterine atony (Table 3). The active management of the third stage of labour has been shown to reduce the risk of PPH by 40% [4].

If bleeding persists, the patient should be transferred for surgical management.

Surgical management [8]

- Examination under anesthesia
- Direct uterine message
- Uterine packing/tamponade
- Compression sutures
- Pelvic devascularization (ligation of the uterine arteries-tubal branches of both ovarian arteries-internal iliac arteries)
- Hysterectomy

This study aims to the treatment and reduction of PPH.

Material and methods

The goal of this study is to demonstrate a new possible prophylactic therapy against PPH, by administering Misoprostol and, if necessary, prostaglandin F2a after vaginal delivery or CS.

This study took place in Athens, Greece (Mitera and Rea hospitals) during the period 1990-2018. The cases included in the study were divided into 2 groups.

- In the first group (1990-2002), 540 childbirths were included (335 normal deliveries and 205 CS). No prophylactic administration of Misoprostol or prostaglandin F2a has been performed in this group.
- In the second group (2003-2018), 875 childbirths were included (498 normal deliveries and 377 CS). Prophylactic administration of Misoprostol and, if necessary, the additional administration of prostaglandin F2a has been performed in this group.

Statistical results and further detailed investigation

1st study group including 540 childbirths (1990-2002) without the prophylactic administration of misoprostol or prostaglandin F2a.

The women's features of this group are included in Table 4.

Out of 540 childbirths, CS account for 205 (38%) and normal deliveries for 335 (62%).

As uterine stimulants, 10 IU of oxytocin and 0.5mg of ergometrine were administered.

a) Significant blood loss (PPH) and haematocrit (HCT) decrease of more than 10% occurred in **16** normal deliveries out of the total 355 (Table 5).

   PPH cases after normal delivery were managed with the administration of additional 40 IU in 500 ml n/saline at a rate of 125 ml/hour (10 IU/hour). Each of 6 women received 4 units of blood. 10 women were treated conservatively (uterine tamponade)

b) Significant blood loss (PPH) and haematocrit (HCT) decrease of more than 10% occurred in **14** CS cases out of the total 205 (Table 5). Two cases suffered from placenta praevia.

   PPH cases after CS were managed with the administration of additional 40 IU in 500 ml n/saline at a rate of 125 ml/hour (10 IU/hour). One woman underwent obstetric hysterectomy without ovaries. Each of four and six women received six units and four units of blood respectively. Three women were treated conservatively.

2nd study group including 875 childbirths (2003-2018) with the prophylactic administration of Misoprostol and, if necessary, the additional administration of prostaglandin F2a.

This group included 875 women who gave birth with CS or vaginal delivery (Table 6) and were treated with the prophylactic administration of prostaglandins. Women with cardiological and/or respiratory disorders and cases with a history of hypertension and allergies were excluded from the study.

Out of 875 childbirths, CS accounted for 377 (43%) of the deliveries while 498 (57%) were vaginal births.

Table 3. Pharmacological management of postpartum haemorrhage [8]

DRUG	DOSE
Oxytocin	5-10 IU IM bolus (if not given at delivery)
Oxytocin infusion	40 IU in 500 ml normal saline at a rate of 125 ml/hour (10 IU/hour)
Ergometrine	0.5 mg IM or IV* (Avoid in: Hypertension, Preeclampsia, Cardiovascular Disease)
Prostaglandin F2 alpha	250 mcg IM can be given every 15 minutes up to a maximum of 8 doses (2 micrograms) or a single dose 2 mg (effective in most patients)
Misoprostol	800 – 1000 micrograms can be administered rectally: 4 or 5 tablets

Table 4. Women's features of the group treated without the prophylactic administration of misoprostol +- PGF2α

Maternal age: 29 years old (average)		
Bleeding history during pregnancy: 48 labours (9%)		
Obstetric history (labours)	**n**	**%**
Primigravida	265	49
Gravida 2	243	45
Gravida 3	32	6
Total	540	100

Table 5. Cases with postpartum haemorrhage after normal delivery and after caesarean section

	Normal delivery	**Caesarian section**
Primigravida:	5	3
Gravida 2:	3	5
Gravida 3:	8	6
Total	**16**	**14**
Bleeding history during pregnancy:	3	2

a) Significant blood loss (PPH) occurred in **21** normal deliveries.

In this group: 1) No more than 10% decrease of haematocrit was observed postoperatively, except in two cases. 2) Just one case received 2 blood units and minor lochia rubra were observed for 24-72 hours. 3) No invasive procedure was performed (including obstetric hysterectomy), neither uterine tamponade nor transfer in the operation room. Out of the aforementioned 21 normal deliveries, from the onset of blood loss (PPH), a single dose of 2mg F2a prostaglandin was administered intracervically for uterine atony. The appropriate genitourinary examination was already performed. As uterotonic agents, a single dose of 10 IU oxytocin and 0.5 mg ergometrine were given (this differs from the CS cases described previously where 600 mg misoprostol was administered rectally after the fetal delivery).

b) Significant blood loss (PPH) occurred in **27** CS cases, including 4 cases with placenta praevia. In one of placenta praevia cases, the woman´s medical history included cryoglobulinemia and 8.2 g Hb preoperatively. After the CS, this patient did not need to receive any blood. Another case with placenta praevia (percreta), after CS, an Asherman syndrome became obvious after the delivery of the fetus. The patient had a medical history of recurrent abortions during the second trimester. Furthermore, a uterine body with partial myometrial deficit was observed (half of the uterine cavity had a strong adhesion partially attached to the endometrium and partially attached to the uterine serosa). The greater part of the invasive placenta (2/3 of its surface) was impossible to be detached. The transfusion requirements for that patient were 2 blood units. The woman was discharged from the hospital the 4th postoperative day and she took antibiotics and uterotonic agents for 30 days. For 45 days, she was expelling retained placental products. Sixty days later, her uterus had returned to a normal size and, according to an ultrasound examination, the strong adhesions of the uterine cavity (observed during the surgery) were resolved.

In one case, after twin delivery with CS, the operation was accompanied by massive obstetric haemorrhage (with an initial haemoglobin of 13.5 g Hb). In more detail, after the delivery of fetuses - placentas, and the uterus positioned out of the abdominal cavity, a massive bleeding surface was observed at the uteral implantation site of the placenta on the posterior wall of the uterus. Thirty seconds after immediate infusion of F2a (given on different parts of the bleeding surface), the torrential bleeding picture "dried out", even though the incision of the uterus was still open, and the uterus was not contracted. The patient came out of the operating room with 8.5 g Hb. Due to this case, F2a has been recommended to be available for immediate use in surgery.

For the PPH cases which were performed with CS, 600 mg misoprostol was administered rectally, simultaneously with the uterine transverse incision. The 4 placenta praevia cases, of which 1 was percreta, were treated with 1000 mg misoprostol rectally, simultaneously with the uterine transverse incision. The average time of delivery of the fetus was 5 minutes after the CS induction. From the onset of blood loss (PPH), a single dose of 2 mg F2a was administered on the bleeding surface of the uterus, followed by immediate closure of the incision [9].

The combination of misoprostol [10-12] that causes severe maternal contractions and prostaglandin F2a [9] that causes severe vasospasm, provided us with excellent control of excessive blood loss (PPH) in normal births and CS (Table 7).

Table 6. Women's features of the group treated with the prophylactic misoprostol and +-PGF2α

Maternal age: 31 years old (average)		
Bleeding history during pregnancy: 87 labours (10%)		
Obstetric history (labours)	**n**	**%**
Primigravita	507	58
Gravida 2	342	39
Gravida 3	26	3
Total	857	100

Table 7. Cases with postpartum haemorrhage after normal delivery and after caesarean section

	Normal delivery	**Caesarean section**
Primigravida	8	6
Gravida 2	4	8
Gravida 3	9	13
Total	**21**	**27**
Bleeding history during pregnancy	3	4

Discussion

Most PPHs occur within 24 hours following labour and that possibility is greater after caesarean deliveries. Without appropriate measures (medical and/or surgical) to minimize blood loss, maternal exsanguination could occur rapidly. Considering that one in two of early PPH cases are due to uterine atony, strategies to treat early PPH first must ensure uterine contraction. The identification and repair of possible genital tract injuries, the management of retained placenta/membranes and the diagnosis and treatment of coagulation failure are included in possible next steps of PPH treatment. Considering that obstetric haemorrhage is associated with significant mortality, rapid diagnosis and treatment are necessary in every case of PPH.

A drawback of our study is that we did not study the effectiveness of misoprostol according to different stratifications of our data. As an example, apart from "classic" risk factors related to PPH, other purported risk factors, such as body mass index [13] could be further investigated if available in patients' medical histories). However, although the material of our study was not derived from national data, a relatively big number of patients was included compared to similar studies [14,15]. Finally, it must be emphasized that although many risk factors for PPH have been identified, not all of them can be used for prevention of PPH in a clinical context [16].

Conclusion

The prophylactic administration of prostaglandins (misoprostol and, if necessary, the additional administration of prostaglandin F2a) is effective in the prevention of postpartum haemorrhage resulting in a lower decrease of postoperative haematocrit without the need for blood transfusion or invasive procedures.

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