ACTIVE MANAGEMENT OF THE THIRD STAGE OF LABOR

W. Prendiville and M. O’Connell

THE EVIDENCE

Traditionally, the third stage of labor is defined as that time between the delivery of the baby and delivery of the placenta. Separation of the placenta from the uterine wall results from a combination of capillary hemorrhage and uterine muscle contraction. The length of the third stage of labor, and its subsequent complications, depends on a combination of the length of time it takes for placental separation and the ability of the uterine muscle to contract.

Preventive clinical management of the third stage of labor varies from the purely expectant to an active approach, or some variation thereof. The expectant (‘pure’ physiological) approach involves waiting for clinical signs of placental separation (alteration of the form and size of the uterus, descent and lengthening of the umbilical cord and blood loss) and allowing the placenta to deliver either unaided using gravity or with the aid of nipple stimulation, as described in most maternity books. In contrast, the full active approach involves administration of an oxytocic agent, early umbilical cord clamping and division and controlled cord traction for delivery of the umbilical cord.

In daily practice, the term ‘active management’ does not mean the same thing to all health-care professionals. Marked variation in practice is seen. A recent survey of management of the third stage of labor in 14 European countries confirmed this variation. Whereas all units professed to practice active management of the third stage of labor, prophylactic uterotonic agents were infrequently employed in units in Austria and Denmark. Controlled cord traction was almost universally used in Ireland and the UK, but in less than 50% of units in the other 12 countries surveyed. Policies with respect to clamping and cutting the umbilical cord also varied widely, with most practitioners clamping and cutting immediately. However, this procedure was not performed in most units in Austria, Denmark, Finland, Hungary and Norway until the cord stopped pulsating.

[Editor’s note: to add to this confusion, there is some concern that early clamping may deprive the neonate of an important amount of blood and its associated hemoglobin, a factor of great importance in many countries of the world. The components of AMTSL, as outlined in the November 2003 Joint Statement of the International Confederation of Midwives (ICM) and the International Federation of Gynecology and Obstetrics (FIGO), are administration of a uterotonic agent (oxytocin is the drug of choice), controlled cord traction, and uterine massage, after delivery of the placenta. See further discussion below.]

Given these circumstances, we reiterate this definition as the combined approach using three component interventions: (1) a prophylactic uterotonic agent; (2) early clamping and division of the umbilical cord; and (3) controlled cord traction.

UTEROTONIC AGENTS

The commonly used uterotonic agents are divided into three groups: oxytocin and oxytocin agonists, ergot alkaloids and prostaglandins.

Oxytocin

Oxytocin (Syntocinon) is a cyclic nonapeptide that is obtained by chemical synthesis. This synthetic form is identical to the natural hormone that is stored in the posterior pituitary and released into the systemic circulation in response to suckling and labor. Oxytocin
stimulates the smooth muscle of the uterus, more powerfully towards the end of pregnancy, during labor, and immediately postpartum. At these times, the oxytocin receptors in the myometrium are increased. The oxytocin receptor is coupled via G-proteins to phospholipase C. The resultant activation triggers release of calcium from intracellular stores and thus leads to myometrial contraction.

Low-dose intravenous infusion of oxytocin elicits rhythmic uterine contractions similar in frequency, force and duration to those observed during labor. Higher infusions can cause sustained uterine contractions. A transient relaxation of smooth muscle, with an associated brief episode of hypotension, flushing and reflex tachycardia, has been observed with rapidly administered intravenous bolus injections.

Oxytocin acts rapidly, with a latency period of less than 1 min after intravenous injection and 2–4 min after intramuscular injection. When oxytocin is administered by a continuous intravenous infusion, the uterine response begins gradually and reaches a steady state within 20–40 min. Removal of oxytocin from plasma is accomplished mainly by the liver and kidneys, with less than 1% excreted unchanged in urine. The metabolic clearance rate amounts to 20 ml/kg/min in the pregnant woman.

The prophylactic use of oxytocin in the third stage of labor has been described in a Cochrane review, where oxytocin alone was compared to no uterotonics and also compared to ergot alkaloids.

### Oxytocin vs. no uterotonics

Seven trials including more than 3000 women were described in this comparison. Variation was noted not only in sample size and dose of oxytocin used, but also in mode of administration, with the intramuscular route being used in three trials and the intravenous route used in the other four trials. Those who received prophylactic oxytocin had clear benefit in terms of postpartum hemorrhage (Figures 1 and 2).

Although debate surrounds the precise definition of postpartum hemorrhage, this benefit was seen whether the cut-off was taken as > 500 ml (relative risk (RR) 0.5, 95% confidence interval (CI) 0.43–0.59) or > 1000 ml (RR 0.61, 95% CI 0.44–0.87). A trend towards a decreased need for therapeutic oxytocin was also demonstrated (RR 0.50, CI 0.39–0.64) in those who received prophylactic oxytocin. A non-statistically significant trend was also seen in the need for manual removal of the placenta in the prophylactic oxytocin group (RR 1.17, 95% CI 0.79–1.73) as well as an insignificant increase in blood transfusion (RR 1.30, 95% CI 0.50–3.39).

### Oxytocin vs. ergot alkaloids

Six trials including over 2800 women were described in this comparison. Variation was noted not only in sample size, dose of oxytocin used, and preparation of ergot alkaloid used, but also in the mode of administration, with the intramuscular route being used in one trial.

#### Table 1

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<th>Study</th>
<th>Oxytocin n/N</th>
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<th>Relative risk (fixed) 95% CI</th>
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<td>25/470</td>
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<td>0/5</td>
<td>Not estimated</td>
<td>0.0</td>
<td>Not estimated</td>
</tr>
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<td>Pierre 1992</td>
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<td>Rosschmann 1991</td>
<td>7/28</td>
<td>10/24</td>
<td>2.8</td>
<td>0.60</td>
<td>0.27 [1.33]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
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<td><strong>1611</strong></td>
<td>100.0</td>
<td><strong>0.50</strong></td>
<td><strong>0.43 [0.59]</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: chi-square=18.10 df=4 p=0.001 I²=77.9%
Test for overall effect: z=8.76 p<0.00001

**Figure 1** Comparison of oxytocin vs. no uterotonics (all trials), with outcome of postpartum hemorrhage (clinically estimated blood loss ≥ 500 ml). Cochrane review.
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the intravenous route in four trials\textsuperscript{18,19,22,23} and both intravenous and intramuscular routes in one trial\textsuperscript{24}.

Little differential effects were demonstrated between these two oxytocics (Figures 3 and 4). Ergometrine was associated with more manual removal of the placenta (RR 0.57, 95\% CI 0.41–0.79) and a statistically insignificant tendency towards hypertension (RR 0.53, 95\% CI 0.19–1.58).

Oxytocin agonists

Carbetocin appears to be the most promising of these agents in preventing postpartum hemorrhage\textsuperscript{25}. Carbetocin is a long-acting synthetic octapeptide analogue of oxytocin, with agonist properties and similar clinical and pharmacological properties to naturally occurring oxytocin. It binds to oxytocin receptors and causes rhythmic contractions of smooth muscle of the uterus, increases the frequency of contractions and increases uterine tone. Intramuscular injections of carbetocin provide similar responses to tetanic contractions (in approximately 2 min), as does intravenous administration, but with a longer duration of activity\textsuperscript{26}. Oxytocin agonists for the prevention of postpartum hemorrhage are currently the subject of an additional Cochrane review\textsuperscript{27}.

Syntometrine

Syntometrine is a mixture of 5 IU oxytocin (Syntocinon) and 500 \(\mu g\) ergometrine maleate. Ergometrine is a naturally occurring ergot alkaloid which stimulates contractions of the uterine and vascular smooth muscle. Following administration, it increases the amplitude and frequency of uterine contractions and tone and thus impedes uterine blood flow. Intense contractions are produced and are usually followed by periods of relaxation. Hemostasis is caused by contractions of the uterine wall around bleeding vessels at the placental site.

The vasoconstriction caused by ergometrine involves mainly capacitance vessels, leading to an increase in central venous pressure and blood
pressure. Ergometrine produces arterial vasoconstriction by stimulation of the α-adrenergic and serotonin receptors and inhibition of endothelial-derived relaxation factor release. Uterine contractions are initiated within 1 min of intravenous injection and last for up to 45 min, whilst, with the intramuscular injection, contractions are initiated within 2–3 min and last for 3 h or longer.28–30.

The prophylactic use of ergometrine–oxytocin in the third stage of labor has also been the subject of a Cochrane review, where ergometrine-oxytocin was compared to oxytocin.31

Ergometrine–oxytocin vs. oxytocin

Six trials including 9332 women were described in this comparison. Variation was noted not only in sample size but also in outcomes measured. Maternal outcomes in terms of nausea and vomiting, the need for blood transfusion and blood pressure measurements were considered in four trials.32–35. Manual removal of the placenta was considered in two trials.33,36. All six trials addressed the issue of postpartum hemorrhage, but much variation was seen in the quantification of the amount of blood lost.32–37.

In terms of postpartum hemorrhage, all six trials demonstrated a significantly lower rate of postpartum hemorrhage with ergometrine–oxytocin regardless of the dose of oxytocin used (odds ratio (OR) 0.82, 95% CI 0.71–0.95). Four trials examined the effects of uterotonic on diastolic blood pressure.32–35. Whilst there was a marked difference in the criteria used to ascertain the changes in diastolic blood pressure, a consistent picture, nevertheless, emerges demonstrating an elevation of diastolic blood pressure both with ergometrine–oxytocin and oxytocin. However, the use of ergometrine–oxytocin was associated with a greater rise in blood pressure than when using oxytocin alone (OR 2.40, 95% CI 1.58–3.64).

The incidence of nausea and/or vomiting was addressed in four trials.32–35. In these trials, a greater incidence of these side-effects was noted with ergometrine–oxytocin use compared to oxytocin alone (vomiting: OR 4.92, 95% CI 4.03–6.00; nausea: OR 4.07, 95% CI 3.43–4.84; vomiting and nausea: OR 5.71, 95% CI 4.97–6.57). The same trials studied the incidence of need for blood transfusion and found no difference (OR 1.37, 95% CI 0.89–2.10). In the two trials that addressed the issue of manual removal of the placenta, no significant difference was shown (OR 1.03, 95% CI 0.80–1.33).33,36.

Prophylactic use of ergot alkaloids in the third stage of labor

Ergot alkaloids are amide derivatives of the tetracyclic compound lysergic acid. There are three categories: (1) the ergotamine group: ergotamine, ergosine and isomers; (2) the regorxine group: ergocornine, ergocristine, ergokryptine and isomers; and (3) the ergotamine and isomers.

The ergot alkaloids act as partial agonists or antagonists at adrenergic, dopaminergic and tryptaminergic receptors. All the ergot alkaloids significantly increase the motor activity of the uterus. They produce persistent contractions in the inner zone of myometrium through calcium channel mechanism and actin–myosin interaction, leading to the shearing effect on placental separation. The gravid uterus is very sensitive to
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Ergot alkaloids, and small doses can be administered immediately postpartum to obtain a marked uterine response. The different preparations and routes of administration have been the subject of a number of studies, both for therapeutic and prophylactic use. All ergot alkaloids have qualitatively the same effect on the uterus; ergometrine is the most active and is also less toxic than ergotamine. For this reason, ergometrine and its semi-synthetic derivative methylergometrine have replaced other ergot preparations as uterine-stimulating agents in obstetrics. The injectable forms of both preparations are unstable when stored unrefrigerated and at high temperatures. The oral forms similarly deteriorate within weeks when stored in increased temperatures. Methylergometrine differs little from ergometrine in its pharmacokinetics. Clinical trials have been conducted on the use of ergot alkaloids in the third stage of labor for prevention of postpartum hemorrhage. The use of ergot alkaloids in the third stage of labor compared with no uterotonic drugs and with different routes of administration is again the subject of a Cochrane review.

Prostaglandins

Prostaglandins ripen the cervix by altering the extracellular ground substance, by increasing the activity of collagenase, and by increasing the elastase, glycoaminoglycans, dermatan sulfate, and hyaluronic acid levels in the cervix. They allow for cervical smooth muscle relaxation and increase intracellular calcium, thus facilitating contraction of the myometrium.

Misoprostol is a synthetic analogue of naturally occurring prostaglandin E<sub>1</sub>. It is rapidly absorbed following oral administration and its bioavailability exceeds 80%. Peak plasma levels are reached in 30–60 min, and it is converted to its active misoprostol acid, which has a half-life of 30–60 min. It is metabolized in the liver, and less than 1% of the active metabolite is excreted in the urine. In pregnancy, it is absorbed across the vaginal mucosa. After oral administration, the plasma concentration increases rapidly to reach a peak in 30 min and rapidly declines, whereas with vaginal administration the peak is reached in 1.5 h before steadily declining.

Moreover, the area under the misoprostol concentration vs. time curve is increased, implying greater exposure time.

The prophylactic use of prostaglandins in the management of the third stage of labor has been the subject of a Cochrane review wherein misoprostol was compared to (1) either placebo or no uterotonic; (2) conventional injectable uterotonic; or (3) injectable prostaglandin vs. injectable uterotonic.

**Misoprostol vs. placebo/no uterotonic**

Six trials were included in this comparison. Misoprostol 400 µg was the dose used in three of the trials. A dose of 600 µg was used in an additional three trials. One trial compared doses of 600 µg, and 400 µg with placebo/no uterotonic.

At both doses, misoprostol was either equal or less effective than placebo/no treatment for blood loss of 1000 ml or more and appeared to have a protective effect on the use of additional uterotonics, although this did not reach statistical significance. Misoprostol was, however, associated with more vomiting, shivering, and pyrexia than placebo, and this was dose-related and occurred across the trials.

Rectal misoprostol was compared to placebo in one trial. No statistically significant reduction in blood loss of at least 1000 ml (RR 0.69, 95% CI 0.35–1.37) or need to use additional uterotonic agents (RR 0.70, 95% CI 0.31–1.62) was observed.

**Misoprostol vs. conventional injectable uterotonic**

Fourteen trials were included in this comparison. The trials are heterogeneous in terms of dose of misoprostol used, route of administration and injectable uterotonic used. Overall, the risk of postpartum hemorrhage of at least 1000 ml was higher for the misoprostol group (RR 1.34, 95% CI 1.16–1.55) compared to either intravenous or intramuscular injections of oxytocin.

**Injectable prostaglandins vs. injectable uterotonics**

Seven trials compared injectable prostaglandins with conventional injectable
uterotonics. The trials were heterogeneous, and reliable estimates of outcomes were not possible. The injectable prostaglandins were associated with less blood loss, a shorter duration of the third stage of labor, more vomiting, diarrhea and abdominal pain than conventional uterotonics. [Editor's note: Interested readers should see also Chapter 12 and Section IV, with the tables in Chapter 19.]

EARLY CORD CLAMPING AND DIVISION

The timing of umbilical cord clamping is variable. In the active management of the third stage of labor, early cord clamping is generally carried out in the first 30 s after birth, regardless of the presence or absence of cord pulsations. Late cord clamping constitutes expectant management, whereby clamping is deferred until cord pulsations have ceased. A precise definition of early or late cord clamping is not currently available.

Delayed clamping of the cord facilitates placental transfusion. This results in an increase in infant blood volume by 30% and an increase in hematocrit and hemoglobin levels, with a resultant increase in iron stores and less anemia in infancy. However, the benefits associated with this increase in infant blood volume are short-lived, lasting no longer than 3 months. In Rhesus-negative women, early clamping of the cord may increase the likelihood of fetomaternal transfusion and so exacerbate the risk of isoimmunization. Early clamping of the cord has also been associated with a higher risk of respiratory distress syndrome in pre-term infants. At present, evidence is insufficient to recommend early or late cord clamping, and the issue is the subject of a Cochrane review.

COMPARISON OF ACTIVE VERSUS EXPECTANT MANAGEMENT

As noted above, the active management of the third stage of labor consists of three interlocking interventions: a prophylactic uterotonics agent, early clamping and division of the umbilical cord, and controlled cord traction.

This management package has been compared to expectant management of the third stage of labor in a Cochrane review. Five trials were included in the analysis. Active management was routinely practiced in the first four of these trials, and both active and expectant management were practiced in the fifth trial. The oxytocins used included oxytocin alone, ergometrine alone and a combination of oxytocin and ergometrine.

The incidence of postpartum hemorrhage both at the 500 ml (RR 0.38, 95% CI 0.32–0.46) and 1000 ml (RR 0.33, 95% CI 0.21–0.51) levels was significantly decreased in the actively managed group compared to the expectantly managed group (Figures 5 and 6). More importantly, the need for blood transfusion was also significantly less in the actively managed group (RR 0.34, 95% CI 0.22–0.53), and the duration of the third stage of labor was not unexpectedly of shorter duration in the actively managed group (RR 0.15, 95% CI 0.12–0.19). A tendency toward an increase in

<table>
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<th>Study</th>
<th>Treatment n/N</th>
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<td>3158</td>
<td>100.0</td>
<td>0.38 [0.32, 0.46]</td>
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Figure 5 Comparison of active vs. expectant management (all women), with outcome of postpartum hemorrhage (clinically estimated blood loss ≥ 500 ml)
the need for manual removal of the placenta was noted in the actively managed group (RR 1.21, 95% CI 0.82–1.78), but this did not reach statistical significance. The incidences of nausea and vomiting were increased in the actively managed group (RR 1.83, 95% CI 1.51–2.23 and RR 2.19, 95% CI 1.68–2.86, respectively). However, this was only noted where ergometrine was used as the oxytocic.

Based on the data presented above, the authors conclude that active management is superior to expectant management in terms of blood loss and other serious complications of the third stage of labor, and that active management should be routine for women expecting a vaginal delivery in a maternity hospital.

[Editor’s note: At the International Conference on the Prevention of Post Partum Hemorrhage held in Goa on July 12–15, 2006, there was considerable discussion on the appropriateness of this intervention to be performed in the hands of skilled birth attendants who were working in a domiciliary delivery, although it was recognized that all such individuals would not have access to an injectable uterotonic for logistic reasons.]

The European 5th Framework has funded an expert group from 14 European Union (EU) countries to address postpartum hemorrhage in the EU. The group reviewed the literature, surveyed participants with respect to current protocols and devised a consensus document89. This group also clarified the definition of active management of the third stage of labor. The consensus document has received wide support from a large number of international authorities and forms the basis for future comparative research and audit. It is reproduced in full as an Appendix to this chapter.

References

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<table>
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<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
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<th>Weight [%]</th>
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Total (95% CI) 3126 3158
Total events: 27 (Treatment), 83 (Control)
Test for heterogeneity chi-square=55.29 df=3 p=0.127
Test for overall effect z=5.07 p<0.00001

Figure 6 Comparison of active vs. expectant management (all women), with outcome of severe postpartum hemorrhage (clinically estimated blood loss ≥1000 ml)83


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60. Ng PS, Chan ASM, Sin WK, Tang LCH, Cheung KB, Yuen PM. A multicentre randomized trial of oral misoprostol and i.m. symmetrine in the management of the third stage of labour. Hum Reprod 2001;16:31–5
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89. Euphrates group. European consensus on prevention and management of postpartum haemorrhage. 2006, in press
APPENDIX: EUROPEAN CONSENSUS ON PREVENTION AND MANAGEMENT OF POSTPARTUM HEMORRHAGE

The EUPHRATES group (EUropean Project on obstetric Haemorrhage Reduction: Attitudes, Trial, and Early warning System), European Union 5th Framework

INTRODUCTION

The EUPHRATES study comprises five parts, the second of these being ‘the development of a minimal European core consensus on prevention and management of post partum hemorrhage’. This consensus is not a protocol or guideline. It represents a European consensus on what could be agreed on by all. Each maternity unit should have its own written protocol concerning prevention and treatment of postpartum hemorrhage (PPH).

Method

This consensus is based on three pillars: (a) review of literature, (b) survey of present protocols and practice, (c) consensus by experts gathered in a special board (see list of members at the end of this Appendix).

The following principle was followed. Where solid evidence was available (level of evidence = 1), a consensus process was not necessary. Consensus was necessary in two circumstances: disagreement as to the clinical relevance of an outcome measure clearly shown to be affected by an intervention (e.g. active management of third stage) and situations where action has to be taken but no high-level evidence is available (e.g. medications in presence of continuing postpartum hemorrhage).

STATEMENTS

1. General considerations

1(a) Definition of postpartum hemorrhage in terms on milliliters lost

Evaluation of blood loss is unreliable. Action is often taken following maternal signs (e.g. hypotension, malaise) rather than on estimated blood loss.

Blood loss at Cesarean section is generally greater than at vaginal delivery.

Despite these three caveats, our group endorses the following classical definitions:

- $\geq 500 \text{ ml} = \text{ postpartum hemorrhage}$
- $> 1000 \text{ ml} = \text{ severe postpartum hemorrhage}$
- $\leq 24 \text{ h} = \text{ primary, or early, postpartum hemorrhage}$
- $> 24 \text{ h} = \text{ secondary, or late, postpartum hemorrhage}$

In regions and in groups where anemia of pregnancy is prevalent, the recognition of lesser amounts is clinically important.

1(b) Communication

Substandard care is often related to lack of communication within the team and between the team and other professionals. Managing difficult cases as a team may make the difference between life and death. Identified communication problems include the following:

- Failure by the first-line care providers to call senior colleagues in time
- Reluctance of senior colleagues to come, when informed of problem
- Failure by the obstetrical team to inform on time other specialists, e.g. intensive care, anesthesiology, hematology.
- In theater, failure of anesthesists and obstetricians to keep each other informed of relevant events, such as rapid blood loss, tachycardia, blood pressure support
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- Caregivers should be trained to be proficient in active third-stage management, and to offer it to all women.
- It is acknowledged, however, that, provided the woman and caregiver are fully informed, a decision not to use active management in some individual cases and/or settings should not be considered substandard care.

1(c) Implementing local policies to ensure rapid availability of blood products at all times

It is mandatory that appropriate blood products be available easily and rapidly in units where women deliver. Different European countries achieve this through different systems and there is no evidence that one system should prevail.

There should be a written document, detailing how this is to be implemented and including practical information such as transfusion department phone number, etc. This document should be widely disseminated.

1(d) Audits and enquiries

The impact of existing guidelines/consensus statements on severe maternal hemorrhage should be monitored by audit and/or confidential enquiries.

2. Prevention of postpartum hemorrhage at vaginal birth

2(a) Active management of the third stage of labor

- Active management of the third stage of labor is usually defined as a three-component intervention: (1) prophylactic uterotonic, (2) early (or less early) clamping of cord, and (3) controlled cord traction. Active management in the third stage of labor has been proven to be effective in reducing blood loss in all women.

The full package of active management is certainly a valid (and validated) option.

- Isolated uterotonics may also be a useful option.

Our group concludes:

- Oxytocin is the first drug of choice for all women in the third stage of labor.
- Syntometrine may be preferred by some clinicians but is contraindicated in hypertension and pre-eclampsia.
• Additional ergometrine (following the administration of oxytocin) in selected cases is considered acceptable practice.

• Misoprostol, although less effective, may be considered in situations where injectable uterotonic drugs are not available.

(ii) Dosage

• Oxytocin: most trials have used intramuscular (IM) or intravenous (IV) administration of 5 or 10 IU of oxytocin. The European survey shows this dosage to be widely practiced. Particular dosages have been reported in various settings, e.g. 20 IU in 500 ml IV bolus or lower doses such as 1 IU in 10 min ("turning up the drip").

• For Syntometrine, there is only one dosage: ergometrine 500 µg with oxytocin 5 units (Syntometrine® 1 ml contained in one ampoule).

• Misoprostol: most trials have used 400–600 µg when administered orally, and 400 µg per rectum.

(iii) Route of administration

• Oxytocin: If an IV line is in situ, the intravenous route is the route of choice. ‘Turning up the drip’ delivers low quantities, e.g. 1–2 IU (1000–2000 mU) in 10 min. If no IV line, IM administration is preferable.

• Syntometrine/Ergometrine: Intramuscular administration.

• Misoprostol can be administered orally or intrarectally.

(iv) Speed of administration

A case of maternal death in the 1997–1999 UK Confidential Enquiry was attributed to severe hypotension following rapid administration of 10 IU oxytocin IV. A key recommendation was made that the administration should be ‘slow’. However, no definition of ‘slow’ is available.

(v) Timing of administration

A recommendation often made, among others in the British National Formulary, is to administer prophylactic oxytocic therapy ‘on (= just after) delivery of the anterior shoulder’, and that is also the timing in use in many randomized trials. In practice, it is reported in our survey that it is usually administered after delivery of the baby. Two randomized, controlled trials compared oxytocin given before and after the placenta had delivered, and found no benefit in providing the uterotonic as early as possible. Further research is needed.

Our group concludes:

• The best time to administer prophylactic oxytocic therapy is just after birth.

• Whether it is administered before or after cord pulsation has ceased seems relatively unimportant.

2(c) Manual removal of the placenta

• Should be performed without delay in presence of hemorrhage.

• No European consensus could be obtained as to when this should be performed in the absence of bleeding. Some would act after 20 min while others would wait for more than 1 hour. Evidence is lacking and further research is needed.

2(d) Other

Nipple stimulation or early breastfeeding have been advocated for prevention of postpartum hemorrhage, as simple and physiological, in particular in low-resource settings. The available evidence from two randomized controlled trials is insufficient to reach a conclusion.

3. Prevention of postpartum hemorrhage at Cesarean section

• For women undergoing delivery by Cesarean section, there is an increased risk that blood transfusion may be necessary.

• It is reasonable to advise routine administration of an uterotonic drug immediately after the baby has been born by Cesarean section.

• Accurate blood loss assessment at Cesarean section is difficult. Measuring both vaginal as
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well as abdominal blood loss may increase accuracy.

- For Cesarean sections that are considered to be at greater risk of hemorrhage (e.g. placenta previa, especially in the presence of uterine scar), it is recommended that a senior obstetrician be present.

4. Management of postpartum hemorrhage

4(a) Postpartum hemorrhage after vaginal delivery

We divided the event into three stages: (i) concern about possible excessive bleeding, (ii) early management of hemorrhage, and (iii) continuing hemorrhage.

(i) Concern about possible excessive bleeding

- If relevant, remove placenta
- Empty bladder, massage uterus until it is well contracted, give additional uterotonic
- Look for any obvious bleeding in episiotomy or tear, and act on findings.

(ii) Immediate management in case of hemorrhage

- Call for help
- Measure blood loss, blood pressure, and pulse rate, insert large gauge intravenous infusion if not yet in place and take blood samples
- Check the placenta for completeness

(iii) If bleeding continues

- Circulatory support as necessary with colloids, colloids and/or blood products
- Ensure appropriate care with sufficient staff or appropriate referral
- Administer additional uterotonic drugs (injectable prostaglandins)
- Perform bimanual compression (time awareness)
- Explore under anesthesia the genital tract for retained placenta or part thereof, or traumatic damage and act on findings.

Whether an anesthetist is available immediately and whether the woman has got an effective epidural will determine the order in which the above and the following occur.

- Keep communication open with the anesthetist and the rest of the team.

(iv) If bleeding still not controlled

- Circulatory support as necessary with colloids and/or blood products, and vasopressors if needed
- Ensure appropriate oxygenation
- Monitor for coagulation abnormalities
- Uterine packing or intrauterine balloon
- Uterine artery embolization

4(b) Hemorrhage at Cesarean section

(i) Immediate management

- Ensure bladder is empty.
- Explore the uterine cavity and remove the placenta and/or clots
- Massage uterus until well contracted, give additional uterotonic
- Look for and repair trauma, consider exteriorization of uterus
- Measure blood loss

(ii) Hemorrhage not controlled

- Continue circulatory support as necessary with colloids and/or blood products and vasopressors if needed
- Ensure appropriate oxygenation and consider mechanical ventilation when needed
- Ensure appropriate care with sufficient staff
- Additional uterotonic drugs (injectable prostaglandins)
- Appropriate surgery

4(c) Factor VII

Recombinant activated factor VII (NovoSeven®) may be a future option in catastrophic
hemorrhage, permitting sometimes to avoid hysterectomy. At present, NovoSeven is very expensive and its safety has not yet been adequately evaluated. Therefore, the use of this drug should be limited to units with adequate expertise and resources, and participating in ongoing registers of use.

Consensus Special Board
The Special Board was made up of experts from 14 European countries:

- **Austria**: Mathias Klein (Obstetrician), Heinz Leipold (Obstetrician); **Belgium**: Sophie Alexander (Obstetrician, Epidemiologist), Paul Defoort (Obstetrician), Corinne Hubinont (Obstetrician), Wei Hong Zhang (Epidemiologist); **Denmark**: Jens Langhoff-Roos (Obstetrician), Desiree Rosenborg (Anesthetist); **Finland**: Risto Erkkola (Obstetrician), Vedran Stefanovic (Obstetrician), Jukka Uotila (Obstetrician); **France**: Marie-Hélène Bouvier-Colle (Epidemiologist), Gérard Breart (Epidemiologist), Catherine Deneux (Epidemiologist), Thierry Harvey (Obstetrician), Frédéric Mercier (anesthetist); **Hungary**: Istvan Berbik (Obstetrician), Jeno Egyed (Obstetrician), Janos Herczeg (Obstetrician); **Ireland**: Mikael O’Connell (Obstetrician), Walter Prendiville (Obstetrician); **Italy**: Anna Maria Marconi (Obstetrician), Graziella Sacchetti (Obstetrician); **Netherlands**: Kathy Herschderfer (Midwife), Jos Van Roosmalen (Obstetrician); **Norway**: Bente Ronnes (Midwife), Babill Stray-Pedersen (Obstetrician); **Portugal**: Diogo Ayres-de-Campos (Obstetrician), Nuno Clode (Obstetrician), Teresa Rodrigues (Obstetrician); **Spain**: Enrique Barrau (Obstetrician), Vicenç Cararach (Obstetrician), Dolores Gomez (Obstetrician); **Switzerland**: Olivier Irion (Obstetrician), Carolyn Troeger (Obstetrician); **United Kingdom**: Zarko Alfirevic (Obstetrician), Peter Brocklehurst (Obstetrician, Epidemiologist), Alison MacFarlane (Epidemiologist), Jane Rogers (Midwife), Clare Winter (Midwife).

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