14

Active Management of the Third Stage of Labor

M. P. O'Connell

THE EVIDENCE

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

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 a modest gush of blood) and allowing the placenta to deliver either unaided using gravity or with the aid of nipple stimulation, as described in most maternity books[1,2]. 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[3–6].

In daily practice, the term 'active management' does not mean the same thing to all health care professionals, and marked variations in practice regularly occur. A recent survey of management of the third stage of labor in 14 European countries confirmed such variations[7]. Whereas all units professed to practice active management of the third stage of labor, prophylactic uterotonics were infrequently employed in units in Austria and Denmark. Controlled cord traction was almost universally practiced in Ireland and the UK, but took place 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 was not the case in many units in Austria, Denmark, Finland, Hungary and Norway, where health care personnel waited until the cord stopped pulsating[7]. *[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 active management of the third stage of labor (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), include 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. L.G.K.]*

Given these circumstances, we reiterate the definition of the combined approach as 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[8,9]. The oxytocin receptor is coupled via G9q proteins to phospholipase C. The resultant activation triggers release of calcium from intracellular stores and thus leads to myometrial contraction[10].

Low-dose intravenous infusion of oxytocin elicits rhythmic uterine contractions similar in frequency, force and duration to those observed during labor. Higher-dose infusions, on the other hand, 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[11].

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[12,13]. 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 uterotonic and also compared to ergot alkaloids[14].

Oxytocin vs. no uterotonics

Seven trials including more than 3000 women have been described[15–21]. Variations were noted, not only in sample size and administered dose of oxytocin, but also in mode of administration, with the intramuscular route preferred in three trials[15–17] and the intravenous route four[18–21]. Those who received prophylactic oxytocin had clear benefit in terms of PPH (Figures 1 and 2). Although debate surrounds the precise definition of PPH, this benefit was present whether the cut-off was taken as blood loss of more than 500 ml (relative risk (RR) 0.5, 95% confidence interval (CI) 0.43–0.59) or more than 1000 ml (RR 0.61, 95% CI 0.44–0.87). A trend towards a decreased need for therapeutic oxytocin was also found (RR 0.50, CI 0.39–0.64) in those who received prophylactic oxytocin. It is not feasible to comment on a possible relationship with manual removal of the placenta or the need for a blood transfusion from the data in this review (Figures 1 and 2).

Oxytocin vs. ergot alkaloids

Six trials including over 2800 women were described in this comparison[15,18,19,22–24]. Variation was present, not only in sample size, dose of oxytocin and preparation of ergot alkaloid, but also in the mode of administration, with the intramuscular route being used in one trial[15], the intravenous route in four [18,19,22,23] and both intravenous and intramuscular routes in a single trial[24]. Few 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 PPH[25]. Carbetocin is a long-acting synthetic octapepetide 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 uterine smooth muscle, 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[26].

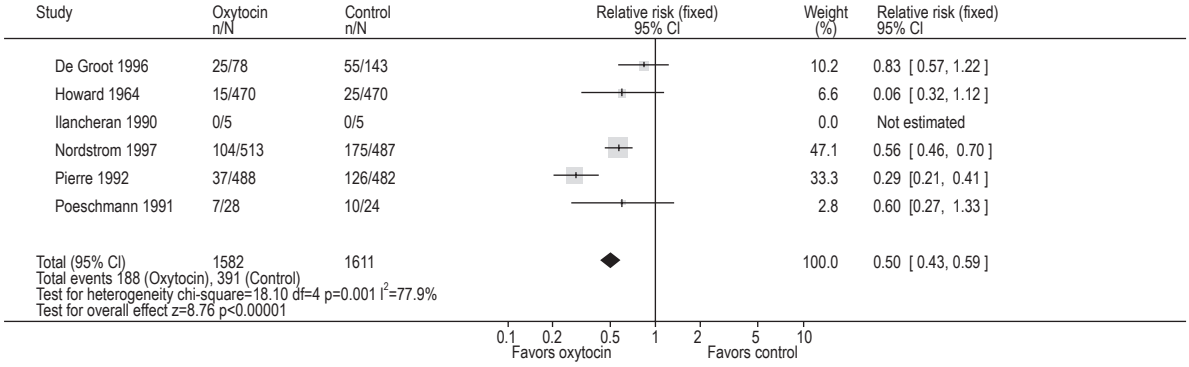

Figure 1 Comparison of oxytocin vs. no uterotonics (all trials), with outcome of PPH (clinically estimated blood loss ≥500 ml). Cochrane review[14]

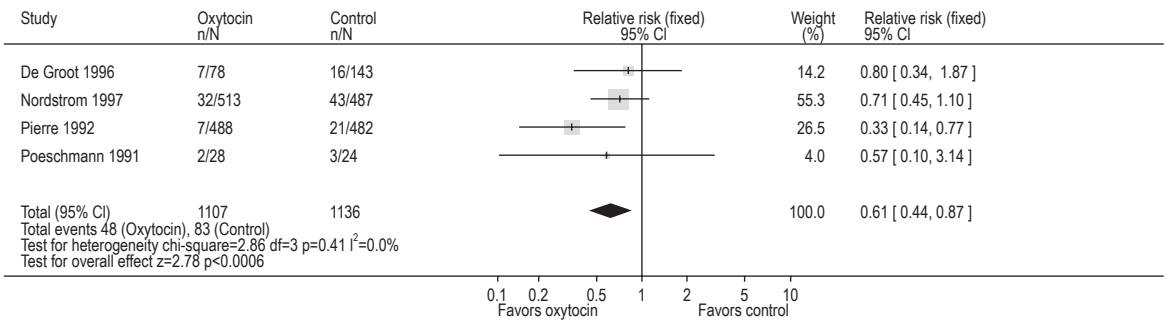

Figure 2 Comparison of oxytocin vs. no uterotonics (all trials), with outcome of severe PPH (clinically estimated blood loss ≥1000 ml). Cochrane review[14]

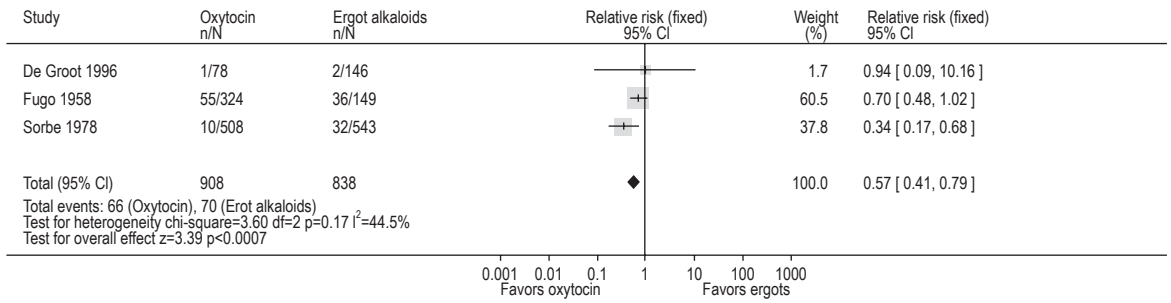

Figure 3 Comparison of oxytocin vs. ergot alkaloids (all trials), with outcome of manual removal of the placenta. Cochrane review[14]

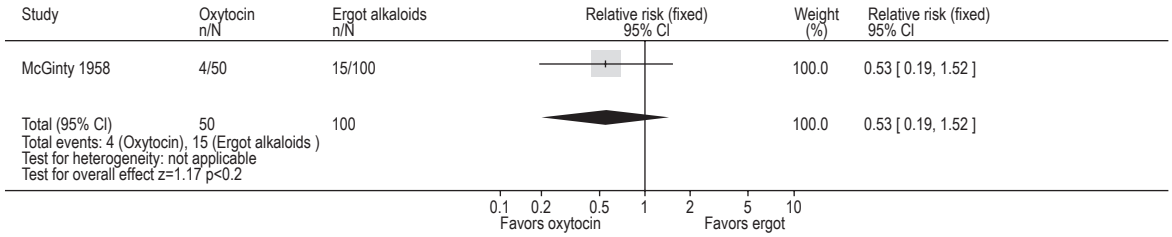

Figure 4 Comparison of oxytocin vs. ergot alkaloids (all trials), with outcome of diastolic blood pressure of more than 100 mmHg between delivery of the baby and discharge from labor ward. Cochrane review[14]

Oxytocin agonists have been compared to conventional uterotonics in a Cochrane review[27]. Three trials[28–30] compared the use of carbetocin and oxytocin for a total of 876 women who received either oxytocin or carbetocin. One trial[31] compared carbetocin with placebo (saline). Here, the use of carbetocin resulted in a statistically significant reduction in the need for therapeutic uterotonic agent (RR 0.44, 95% CI 0.25–0.78) compared to oxytocin for those who underwent cesarean section, but not for vaginal delivery. However, currently there is insufficient evidence to suggest that carbetocin is as effective as oxytocin to prevent postpartum hemorrhage (PPH).

Syntometrine

Syntometrine is a mixture of 5 IU oxytocin (Syntocinon) and 500 μg ergometrine maleate. Ergometrine is a naturally occurring ergot alkaloid which stimulates contractions of uterine and vascular smooth muscle. Following administration, it increases the amplitude and frequency of uterine contractions and tone, thus impeding 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[31–34].

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[35].

Ergometrine–oxytocin vs. oxytocin

Six trials including 9332 women were described in this comparison[36–41]. Variations were noted in sample size and in outcomes measured. Maternal outcomes in terms of nausea and vomiting, the need for blood transfusion and blood pressure changes were considered in four trials[36–41], as was manual removal of the placenta in two trials[37,40]. All six addressed the issue of PPH, but variations were seen in quantification of blood lost[36–41].

In terms of PPH, all six trials[36–41] demonstrated a significantly lower rate 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 uterotonics on diastolic blood pressure[36–39]. 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 with ergometrine–oxytocin or oxytocin administration. However, the use of ergometrine–oxytocin was associated with a greater increase in blood pressure than oxytocin alone (OR 2.40, 95% CI 1.58–3.64).

The incidence of nausea and/or vomiting was addressed in four trials[36–39]. 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). In terms of the need for blood transfusion, the same trials found no difference (OR 1.37, 95% CI

0.89–2.10). The two trials that addressed the issue of manual removal of the placenta found no significant differences (OR 1.03, 95% CI 0.80–1.33)[37,40].

Prophylactic use of ergot alkaloids in the third stage of labor

Ergot alkaloids are amide derivatives of the tetracyclic compound lysergic acid and include three categories: (1) the ergotamine group: ergotamine, ergosine and isomers; (2) the regotoxine 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 producing persistent contractions in the inner zone of myometrium through calcium channel mechanism and actin–myosin interaction that lead to the shearing effect on placental separation. The gravid uterus is very sensitive to ergot alkaloids, whereby small doses administered immediately postpartum result in a marked uterine response. The different preparations and routes of administration have been the subject of a number of investigations, both for therapeutic and prophylactic use[15,42–45]. All ergot alkaloids have the same qualitative 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. Unfortunately, the injectable forms of both preparations are unstable when stored unrefrigerated and at high temperatures. Similarly, the oral forms deteriorate within weeks when stored in increased temperatures. These latter qualities are crucial in determining whether these agents can be used in many parts of the world and are perhaps more important than the pharmacological properties. 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 PPH[15,23,42]. The use of ergot alkaloids in the third stage of labor compared with no uterotonic drugs and with different routes of administration is the subject of a Cochrane review[46]. The authors of this review conclude that prophylactic intramuscular or intravenous injections of ergot alkaloids are effective in reducing blood loss, PPH and the use of therapeutic uterotonics, but adverse effects include elevated blood pressure and pain after birth requiring analgesia, particularly with the intravenous route of administration.

Prostaglandins

Prostaglandins ripen the cervix by altering the extracellular ground substance, increasing the activity of collagenase and increasing the elastase, glycoaminoglycans, dermatan sulfate and hyaluronic acid levels in the cervix[47,48]. These agents 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 E1. 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 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[49].

The prophylactic use of prostaglandins in the management of the third stage of labor is the subject of a Cochrane review wherein misoprostol was compared[50] 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 in three trials[51–53], a dose of 600 μg was used in an additional three trials[54–56], and one trial compared doses of 600 μg and 400 μg with placebo/no uterotonic[57].

At both doses (400 or 600 μg), misoprostol was either equal or less effective than placebo/no treatment for blood loss of 1000 ml or more; it also appeared to have a protective effect on the use of additional uterotonics, although this effect did not reach statistical significance. However, misoprostol was, associated with a triad of non-lethal side effects (more vomiting, shivering and pyrexia than placebo), and this observation was dose-related and occurred across the trials.

Rectal misoprostol was compared to placebo in one trial[53]. 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 uterotonics

Fourteen trials were included in this comparison[55,58–73]. The trials are heterogeneous in terms of dose of misoprostol administered, route of administration and type of injectable uterotonic. Overall, the risk of PPH of at least 1000 ml was higher for the misoprostol group (RR 1.32, 95% CI 1.16–1.51) compared to either intravenous or intramuscular injections of oxytocin[74].

Injectable prostaglandins vs. injectable uterotonics

Seven trials compared injectable prostaglandins with conventional injectable uterotonics[17,45,77–81]. 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 Section 6. L.G.K.]*

EARLY CORD CLAMPING AND DIVISION

The timing of umbilical cord clamping is variable[82]. In the active management of the third stage of labor, early cord clamping is generally carried out in the first 30 seconds after birth, regardless of the presence or absence of cord pulsations[83]. 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[84].

Delayed clamping of the cord facilitates placental transfusion and 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[84–86]. The benefits associated with this increase in infant blood volume are short-lived, however, lasting no longer than 3 months[85]. In Rhesus-negative women, early clamping of the cord may increase the likelihood of fetomaternal transfusion and thus exacerbate the risk of isoimmunization[84]. Early clamping of the cord has also been associated with a higher risk of respiratory distress syndrome in pre-term infants[87]. The recent Cochrane review concludes that delayed cord clamping is not associated with an increase in PPH. However, in neonatal terms, delayed cord clamping is associated with an increase in iron store, albeit with an increase in risk of neonatal jaundice requiring phototherapy[88].

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 uterotonic 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[89]. Five trials were included in the analysis[90–94]. Active management was routinely practiced in the first four, and both active and expectant management were practiced in the fifth trial. The oxytocics used included oxytocin alone, ergometrine alone and a combination of oxytocin and ergometrine.

The incidence of PPH both at the 500 ml (RR 0.34, 95% CI 0.27–0.044) and 1000 ml (0.34, 95% CI 0.14–0.87) 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 0.35, 95% CI 0.22–0.55), and the duration of the third stage of labor was not unexpectedly shorter in the actively managed group (RR 0.15, 95% CI 0.12–0.19).

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

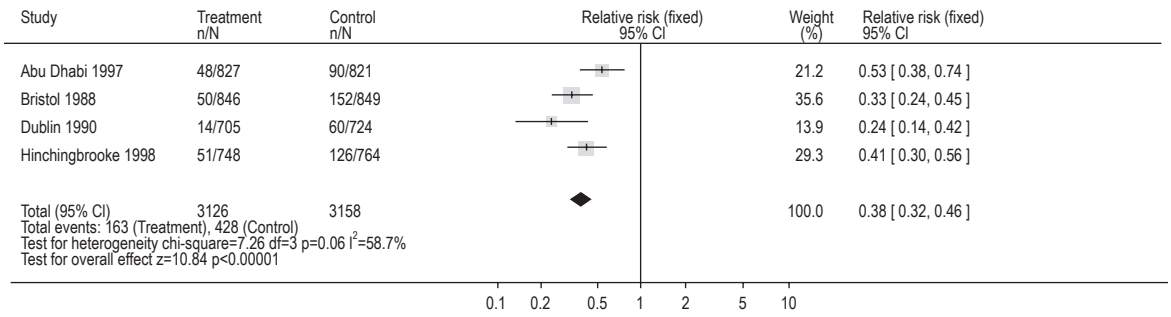

Figure 5 Comparison of active vs. expectant management (all women), with outcome of postpartum hemorrhage (clinically estimated blood loss ≥500 ml)

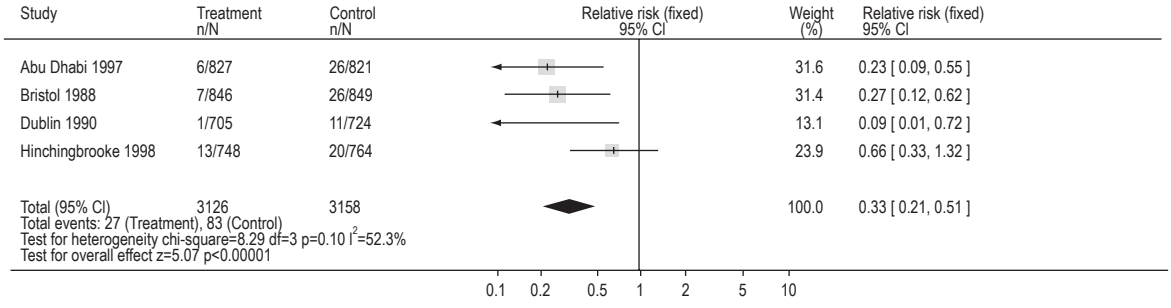

Figure 6 Comparison of active vs. expectant management (all women), with outcome of postpartum hemorrhage (clinically estimated blood loss ≥1000 ml)

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. L.G.K.]*

The European 5th Framework has funded an expert group from 14 European Union (EU) countries to address PPH in the EU. The group reviewed the literature, surveyed participants with respect to current protocols, devised a consensus document[95], and 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 Addendum A to this chapter.

References

1. Sweet D. Mayes Midwifery, 12th edn. London: WB Saunders Co, 1997
2. Stables D. Physiology in Childbearing with Anatomy and Related Biosciences. London: Balliere Tindall, 1999
3. Prendiville WJ, Harding JE, Elbourne DR, Stirrat GM. The Bristol third stage trial: active vs physiological management of the third stage of labour. Br Med J 1988;297:1295–1300
4. Den Hertog CE, DeGroot AN, VanDongen PW. History and use of oxytocics. Eur J Obstet Gynaecol Reprod Med 2001;94:8–12
5. McCormick ML, Sanghvi HC, Kinzie B, McIntosh N. Preventing postpartum haemorrhage in low-resource settings. Int J Gynaecol Obstet 2002;77:267–75
6. World Health Organization. Pregnancy, Childbirth, Postpartum and Newborn Care: a Guide for Essential Practice. Geneva: World Health Organization, 2003
7. Winter C, Macfarlane A, Deneux C, et al. Policies for management of the third stage of labour and the immediate management of postpartum haemorrhage in Europe: what is the role of evidence? BJOG 2007;114:845–54
8. Alexandrova M, Soloff MA. Oxytocin receptors and parturition. I. Control of oxytocin receptor concentration in the rat myometrium at term. Endocrinology 1980;106:730–5
9. Fuchs AR, Fuchs F, Hurstein P, Soloff MS, Fernstrom MJ. Oxytocin receptors and human parturition: a dual role for oxytocin in the initiation of labor. Science (New York) 1982;215:1396–8
10. Sanborn BM, Dodge K, Monga M, Qian A, Wang W, Yue C. Molecular mechanisms regulating the effects of oxytocin on myometrial intercellular calcium. Adv Exp Med Biol 1998;449:277–86
11. Parker SL, Schimmer BP. Pituitary hormones and their hypothalamic releasing hormones. In Goodman and Gilman, eds. The Pharmacological Basis of Therapeutics, 11th edn. New York: McGraw Hill, 2006:1489–510
12. Amico JA, Seitchik J, Robinson AG. Studies of oxytocin in plasma of women during hypocontractile labor. J Clin Endocrinol Metab 1984;58:274–9
13. De Groot AN, Vree TB, Hekster YA, et al. Bioavailability and pharmacokinetics of sublingual oxytocin in male volunteers. J Pharm Pharmacol 1995;47:571–5
14. Cotter AM, Amen Ness A, Tolosa JE Prophylactic oxytocin for the third stage of labour. Cochrane Database Syst Rev 2010;(4):CD001808
15. De Groot ANJA, Van Roosmalen J, Van Dongen PWJ, Borm GF. A placebo-controlled trial of oral ergometrine to reduce postpartum haemorrhage. Acta Obstet Gynecol Scand 1996;75:464–8
16. Newton M, Mosey LM, Egli GE, Gifford WB, Hull CT. Blood loss during and immediately after delivery. Obstet Gynecol 1961;17:9–18
17. Poeschmann RP, Doesburg WH, Eskes TKAB. A randomised comparison of oxytocin, sulprostone and placebo in the management of the third stage of labour. Br J Obstet Gynaecol 1991;98:528–30
18. Howard WF, McFadden PR, Keetek WC. Oxytocic drugs in the fourth stage of labor. JAMA 1964;189:411–13
19. Ilancheran A, Ratnam SS. Effect of oxytocin on prostaglandin levels in the third stage of labour. Gynecol Obstet Invest 1990;29:177–80
20. Nordstrom L, Fogelstam K, Friedman G, Larsson A, Rydhstroem H. Routine oxytocin in the third stage of labour: a placebo controlled randomised trial. Br J Obstet Gynaecol 1997;104:781–6
21. Pierre F, Mesnard L, Body G. For a systematic policy of iv oxytocin where a fairly active management of third stage of labour is yet applied: results of a controlled trial. Eur J Obstet Gynaecol Reprod Med 1992;43:131–5
22. Fugo NW, Dieckmann WJ. A comparison of oxytocic drugs in the management of the placental stage. Am J Obstet Gynecol 1958;76:141–6
23. Sorbe B. Active pharmacological management of the third stage of labor. A comparison of oxytocin and ergometrine. Obstet Gynecol 1978;52:694–7
24. McGinty LB. A study of the vasopressor effects of oxytocics when used intravenously in the third stage of labour. Western J Surg 1956;64:22–8
25. Chong YS, Su LL, Arulkumaran S. Current strategies for the prevention of postpartum haemorrhage in the third stage of labour. Curr Opin Obstet Gynecol 2004;16:143–50
26. Hunter DJ, Schulz P, Wassenaar W. Effects of carbetocin, a long acting oxytocin analog on the postpartum uterus. Clin Pharm Therapeu 1992;52:60–7
27. Su LL, Chong YS, Samuel M. Carbetocin for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2012;(4):CD005457
28. Boucher M, Horbay GL, Griffin P, et al. Double-blind, randomized comparison of the effect of carbetocin and oxytocin on intraoperative blood loss and uterine tone of patients undergoing caesarean section. J Perinatol 1998;18:202–7
29. Boucher M, Nimrod CA, Tawagi GF, Meeker TA, Rennicks White RE, Varin, J. Comparison of carbetocin and oxytocin for the prevention of postpartum haemorrhage following vaginal delivery: a double-blind randomized trial. J Obstet Gynaecol Canada JOGC 2004;26:481–8
30. Dansereau J, Joshi AK, Helewa ME, et al. Double-blind comparison of carbetocin versus oxytocin in prevention of uterine atony after caesarean section. Am J Obstet Gynecol 1999;180:670–6
31. Barton SR, Jackson A. The safety and efficiency of carbetocin to control uterine bleeding following caesarean section. Prenat Neonat Med 1996;1:185
32. Rall TW. Oxytocin, prostaglandins, ergot alkaloids, and other drugs; tocolytic agents. In: Goodman, Gilman A, Rall TW, Nies AS, Taylor P, eds. Goodman and Gilman's The Pharamacological Basis of Therapeutics. Toronto: Pergamon Press, 1990:933–53
33. Berde E, Stürmer E. Introduction to the pharmacology of ergot alkaloids and related compounds as a basis to their therapeutic application. In: Berde B, Schild HO, eds. Ergot Alkaloids and Related Compounds. New York: Springer Verlag, 1978:1–28
34. Müller-Schweinitzer E, Weidmann H. Basic pharmacological propertues. In: Berde B, Schild HO, eds. Ergot Alkaloids and Related Compounds. New York: Springer Verlag, 1978:87–232

35. McDonald S, Abbott JM, Higgins SP. Prophylactic ergometrine-oxytocin versus oxytocin for the third stage of labour. Cochrane Database Syst Rev 2004;(1):CD000201
36. Choy CMY, Lau WC, Tam WH, Yuen PM. A randomised controlled trial of intramuscular syntometrine and intravenous oxytocin in the management of the third stage of labour. Br JObstet Gynaecol 2002;109:173–7
37. Khan GQ, John LS, Chan T, Wani S, Hughes AO, Stirrat GM. Abu Dhabi third stage trial: Oxytocin versus syntometrine in the active management of the third stage of labour. Eur J Obstet Gynaecol Reprod Med 1995;58:147–51
38. McDonald SJ, Prendiville W, Blair E. Randomised controlled trial of oxytocin alone versus oxytocin and ergometrine in the active management of the third stage of labour. Br Med J 1993;307:1167–71
39. Yuen PM, Chan NST, Yim SF, Chang AMZ. A randomised double blind comparison of syntometrine and syntocinon in the management of the third stage of labour. Br J Obstet Gynaecol 1995;102:377–80
40. Nieminen U, Jarvinen PA. A comparative study of different medical treatments of the third stage of labour. Ann Chirurig Gynaecol Fenniae 1963;53:424–9
41. Mitchell GG, Elbourne DR. The Salford third stage trial: oxytocin plus ergometrine versus oxytocin alone in the active management of the third stage of labour. Online J Curr Clin Trials 1993;2:Doc 83
42. Andersen B, Andersen LL, Sorensen T. ethylergometrine during the early puerperium; a prospective randomized double blind study. Acta Obstet Gynecol Scand 1998;77:54–7
43. Borri P, Gerli P, Antignani FL, et al. Methylergonovine maleate: a proposal for its more specific use. Biol Res Preg Perinatol 1986;7:128–30
44. Moir DD, Amoa AB. Ergometrine or oxytocin? Blood loss and side effects at spontaneous vertex delivery. Br J Anaes 1979;51:113–17
45. Van Selm M, Kanhai HH, Keirse MJ. Preventing the recurrence of atonic postpartum hemorrhage: a double blind trial. Acta Obstet Gynecol Scand 1995;74:270–4
46. Liabsuetrakul T, Choobun T, Peeyananjarassri K, Islam QM. Antibiotic prophylaxis for operative vaginal delivery. Cochrane Database Syst Rev 2009;(2):CD004455
47. Uldbjerg N, Ekman G, Malmstrom A, Sporrong B, Ulmstein U, Wingerup L. Biochemical and morphological changes of human cervix after local application of prostaglandin E2 in pregnancy. Lancet 1981;1:267–8
48. Uldbjerg N, Ekman G, Malmstrom A, Olsson K, Ulmstein U. Ripening of the human uterine cervix related to changes in collagen, glycosaminoglycans, and collagenolytic activity. Am J Obstet Gynecol 1983;147:662–6
49. More B. Misoprostol: an old drug, new indications. J Postgrad Med 2002;48:336–9
50. Gülmezoglu AM, Forna F, Villar J, Hofmeyr GJ. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2007;(3):CD000494
51. Hofmeyr GJ, Nikodem VC, deJager M, Gelbart BR. A randomised placebo controlled trial of oral misoprostol in the third stage of labour. Br J Obstet Gynaecol 1998;105:971–5
52. Hofmeyr GJ, Nikodem VC, deJager M, Drakely A, Gelbart B. Oral misoprostol for labour third stage management: randomised assessment of side effects (part 2). Proceedings of the 17th Conference on Priorities in Perinatal care; 1998, South Africa, 1998:53–4
53. Bamigboye AA, Hofmeyr GJ, Merrell DA. Rectal misoprostol in the prevention of postpartum hemorrhage: a placebo controlled trial. Am J Obstet Gynecol 1998;179: 1043–6
54. Surbek DV, Fehr P, Hoesli I, Holzgreve W. Oral misoprostol for third stage of labor: a randomized placebo-controlled trial. Obstet Gynecol 1999;94:255–8
55. Benchimol M, Gondry J, Mention J, Gagneur O, Boulanger J. Role of misoprostol in controlled delivery [Place du misoprostol dans la direction de la deliverance]. J Gynaecol Obstet Biol Reprod 2001;30:576–83
56. Hofmeyr GJ, Nikodem VC, deJager M, Drakely A. Side effects of oral misoprostol in the third stage of labour: a randomised placebo controlled trial. South Afr Med J 2001; 91:432–5
57. Hofmeyr GJ, Nikodem VC, de Jager M, Gelbart BR. A randomized placebo-controlled trial of oral misoprostol in the third stage of labour. Br J Obstet Gynaecol 1998;105:971–5
58. Caliskan E, Dilbaz B, Meydanli M, Ozturk N, Narin MA, Haberal P. Oral misoprostol for the third stage of labor: a randomized controlled trial. Obstet Gynecol 2003;101:921–8
59. Cook C, Spurrett B, Murray H. A randomized clinical trial comparing oral misoprostol with synthetic oxytocin or syntometrine in the third stage of labour. Aust N Z J Obstet Gynaecol 1999;39:414–19
60. Amant F, Spitz B, Timmerman D, Corremans A, Van Assche FA. Misoprostol compared with methylergometrine for the prevention of postpartum haemorrhage: a double-blind randomised trial. Br J Obstet Gynaecol 1999;106:1066–70
61. Lumbiganon P, Hofmeyr J, Gulmezoglu AM, Villar J. Misoprostol dose related shivering and pyrexia in the third stage of labour. Br J Obstet Gynaecol 1999;106:304–8
62. Whalley RL, Wilson JB, Crane JM, Matthews K, Sawyer E, Hutchens D. A double-blind placebo controlled randomised trial of misoprostol and oxytocin in the management of the third stage of labour. Br J Obstet Gynaecol 2000;107:1111–15
63. El-Refaey H, Nooh R, O'Brien P, Abdalla M, Geary M, Walder J, Rodeck C. The misoprostol third stage of labour study: a randomised controlled comparison between orally administered misoprostol and standard treatment. Br J Obstet Gynaecol 2000;107:1104–10
64. Ng PS, Chan ASM, Sin WK, Tang LCH, Cheung KB, Yuen PM. A multicentre randomized trial of oral misoprostol and i.m syntometrine in the management of the third stage of labour. Hum Reprod 2001;16:31–5
65. Bugalho A, Daniel A, Faundes A, Cunha M. Misoprostol for prevention of postpartum haemorrhage. Int J Gynaecol Obstet 2001;73:1–6
66. Lokugamage A, Paine M, Bassaw-Balroop K, et al. Active management of the third stage at Cesarean section: a randomized controlled trial of misoprostol versus syntocinon. Aust N Z Obstet Gynaecol 2001;41:411–14
67. Gerstenfeld TS, WingDA. Rectal misoprostol versus intravenous oxytocin for the prevention of postpartum hemorrhage after vaginal delivery. Am J Obstet Gynecol 2001;185:878–82
68. Gulmezoglu AM, Villar J, Ngoc NT, et al. The WHO multicentre double-blind randomized trial to evaluate the use of misoprostol in the management of the third stage of labour. Lancet 2001;358:689–95
69. Kundodyiwa TW, Majoko F, Rusakaniko S. Misoprostol versus oxytocin in the third stage of labor. Int J Obstet Gynaecol 2001;75:235–41
70. Karkanis SG, Caloia D, Salenieks ME, et al. Randomized controlled trial of rectal misoprostol versus oxytocin in third stage management. J Obstet Gynecol Can 2002;24:149–54
71. Penaranda W, Arrieta O, Yances B. Active management of the childbirth with sublingual misoprostol: a clinical controlled trial in the Hospital de Maternidad Rafeal Calvo. Revista Colomb Obstet Ginecol 2002;53:87–92
72. Caliskan E, Meydanli M, Dilbaz B, Aykan B, Sonmezer M, Haberal A. Is rectal misoprostol really effective in the treatment of third stage of labor? A randomized controlled trial. Am J Obstet Gynecol 2002;187:1038–45
73. Caliskan E, Dilbaz B, Meydanli M, Ozturk N, Narin M, Haberal A. Oral misoprostol for the third stage of labor: a randomized controlled trial. Obstet Gynecol 2003;101:921–8
74. Parsons S, Walley RL, Crane JMG, Matthews K, Hutchens D. Oral misoprostol versus oxytocin in the management of the third stage of labour. J Obstet Gynaecol Canada JOGC 2006;28:20–6
75. Lam H, Tang OS, Lee CP, Ho PC. A pilot-randomized comparison of sublingual misoprostol with syntometrine on the blood loss in third stage of labor. Acta Obstet Gynecol Scand 2004;83:647–50

76. Gulmezoglu AM, Villar J, Ngov NT, et al. WHO multicentre randomized controlled trial of misoprostol in the management of the third stage of labour. Lancet 2001;358:689–95
77. Abdel-Aleem H, Abol-Oyoun EM,Moustafa SAM, Kamel HS, Abdel-Wahab HA. Carboprost trometamol in the management of the third stage of labor. Int J Obstet Gynaecol 1993;42:247–50
78. Bhattacharya P, Devi PK, Jain S, Kanthamani CR, Raghavan KS. Prophylactic use of 15(S) 15 methyl PGF2 alpha by intramuscular route for control of postpartum bleeding – a comparative trial with methylergometrine. Acta Obstet Gynecol Scand 1998;(Suppl 145):13–15
79. Chua S, Chew SL, Yeoh CL, et al. A randomized controlled study of prostaglandin 15-methyl F2 alpha compared with syntometrine for prophylactic use in the third stage of labour. Aust N Z J Obstet Gynaecol 1995;35:413–16
80. Catanzarite VA. Prophylactic intramyometrial carboprost tromethamine does not substantially reduce blood loss relative to intramyometrial oxytocin at routine caesarean section. Am J Perinatol 1990;7:39–42
81. Chou MM, MacKenzie IZ. A prospective, double blind, randomized comparison of prophylactic intramyometrial 15-methyl prostaglandin F2 alpha, 125 micrograms, and intravenous oxytocin, 20 units, for the control of blood loss at elective caesarean section. Am J Obstet Gynecol 1994;171: 1356–60
82. Inch S. Management of the third stage of labour: another cascade of intervention? Midwifery 1991;7:64–70
83. McDonald SJ. Management in the Third Stage of Labour. Western Australia: University of Western Australia, 1996
84. Prendiville WJ, Elbourne D. Care during the third stage of labour. In Chalmers I, Enkin M, Keirse MJNC, eds. Effective Care in Pregnancy and Childbirth. Oxford: Oxford University Press, 1989:1145–69
85. World Health Organisation. Care of the umbilical cord: a review of the evidence. Geneva: World Health Organisation, 1998
86. Mercer JS. Current best evidence: a review of the literature on umbilical cord clamping. J Midwifery Women's Health 2001;46:402–14
87. Rabe H, Reynolds G, Diaz-Rossello J. Early versus delayed umbilical cord clamping in preterm infants. Cochrane Database Syst Rev 2004;(3):CD003248
88. McDonald SJ, Middleton P. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Cochrane Database Syst Rev 2008;(2):CD004074
89. Begley CM, Gyte GM, Murphy DJ, Devane D, McDonald SJ, McGuire W. Active versus expectant management for women in the third stage of labour. Cochrane Database Syst Rev 2010;(7):CD007412
90. Khan GQ, John LS, Wani S, Doherty T, Sibai BM. Controlled cord traction versus minimal intervention techniques in delivery of the placenta: a randomized controlled trial. Am J Obstet Gynecol 1997;177:770–4
91. Thilaganathan B, Cutner A, Latimer J, Beard R. Management of the third stage of labour in women at low risk of postpartum haemorrhage. Eur J Obstet Gynaecol Reprod Biol 1993;48:19–22
92. Prendiville WJ, Harding JE, Elbourne D, Stirrat GM. The Bristol Third Stage Trial: active vs. physiological management of third stage of labour. BMJ 1988;297:1295–300
93. Begley CM. A comparison of active and physiological management of the third stage of labour. Midwifery 1990;6:3–17
94. Rogers J, Wood J, McCandlish R, Ayers S, Truesdale A, Elbourne D. Active vs expectant management of the third stage of labour: the Hitchingbrooke randomised controlled trial. Lancet 1998;351:693–9
95. EUPHRATES group. European consensus on prevention and management of postpartum haemorrhage. 2005. www.euphrates.inserm.fr/inserm/euphrates.nsf/AllDocumentsByUNID/95A14F46F31A5246C125707400485AED?OpenDocument&l = 3.1

Addendum A: European Consensus on Prevention and Management of Postpartum Hemorrhage

*The EUPHRATES group (**EU**ropean **P**roject on obstetric **H**aemorrhage **R**eduction: **A**ttitudes, **T**rial, and **E**arly warning **S**ystem), 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 Addendum). he 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 PPH).

STATEMENTS

1. General considerations

1(a) *Definition of PPH 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:

- ≥500 ml = PPH
- >1000 ml = severe PPH
- ≤24 h = primary, or early, PPH
- >24 h = secondary, or late, PPH

In regions and in groups where anemia of pregnancy is revalent, 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 interventions (fluid replacement and/or vasopressor use), etc.
- Failure to obtain blood, because of lack of perception by the laboratory/blood transfusion staff of the severity of the case

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 PPH 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[1]. The evidence that active routine management reduces severe maternal adverse effects (morbidity) resulting from PPH is less convincing.

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

- Isolated uterotonics may also be a useful option[2].

Our group concludes:

- 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.

2(b) *Type, dosage, route, speed and timing of administration of prophylactic uterotonic drugs*

There is a lack of randomized trials addressing the questions of dosage, route and timing of prophylactic uterotonic drug administration, because most trials have compared the full package made up of three interventions to no intervention.

(i) *Type of drug*

- Oxytocin is the most frequently used drug for active management in Europe.
- In the United Kingdom and Ireland, Syntometrine is widely used. This is a combination of oxytocin and ergometrine. Syntometrine is more effective but is associated with more side-effects than oxytocin[3]. Syntometrine is not suitable for all women, e.g. in hypertension.
- Ergometrine has been reported in the European survey as additional prophylaxis (following the administration of oxytocin), after the placenta has been delivered in women with risk factors such as multiple pregnancy or grand multiparae. This has never been assessed in a randomized trial.
- Misoprostol is less effective than injectable uterotonics in reducing postpartum blood loss; however, its superiority over placebo as part of the active management of the third stage of labor remains uncertain[4].

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 uterotonics 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 5 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 Bristish 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[5,6] 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 PPH, as simple and physiological, in particular in low-resource settings. The available evidence from two randomized controlled trials[7,8] is insufficient to reach a conclusion.

3. Prevention of PPH 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 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 PPH

4(a) *PPH 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 uterotonics
- 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 crystalloids, 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 uterotonics
- 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 (Novo-Seven®) 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);
Nederlands: 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).

References

1. Prendiville WJ, Elbourne D, MacDonald S. Active versus expectant management in the third stage of labour (Cochrane Review). Cochrane Library, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd
2. Elbourne DR, Prendiville WJ, Carroli G, Wood J, MacDonald S. Prophylactic use of oxytocin in the third stage of labour (Cochrane Review). Cochrane Library, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd
3. MacDonald S, Abbott JM, Higgins SP. Prophylactic ergometrine-oxytocin versus oxytocin for the third stage of labour (Cochrane Review). Cochrane Library, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd
4. Villar J, Gülmezoglu AM, Hofmeyr J, Forna F. Systematic review of randomized controlled trials of misoprostol to prevent postpartum hemorrhage. Obstet Gynecol 2002;100: 1301–12
5. Jackson KW Jr, Allbert JR, Schemmer GK, Elliot M, Humphrey A, Taylor J. A randomized controlled trial comparing oxytocin administration before and after placental delivery in the prevention of postpartum hemorrhage. Am J Obstet Gynecol 2001;185:873–7
6. Huh WK, Chelmow D, Malone FD. A double blinded, randomized controlled trial of oxytocin at the beginning versus the end of the third stage of labor for prevention of postpartum hemorrhage. Gynecol Obstet Invest 2004;58:72–6
7. Bullough C, Msuku R, Karonde L. Early sucking and post partum haemorrhage: controlled trial in deliveries by traditional birth attendants. Lancet 1989;334:522–5
8. Irons D, Sriskandabalan, Bullough C. A simple alternative to parenteral oxytocic for the third stage of labour. Int J Gynaecol Obstet 2004;46:15–18