Guidelines

International consensus statement on the use of uterotonic agents during caesarean section

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Summary

It is routine to give a uterotonic drug following delivery of the neonate during caesarean section. However, there is much heterogeneity in the relevant research, which has largely been performed in low-risk elective cases or women with uncomplicated labour. This is reflected in considerable variation in clinical practice. There are significant differences between dose requirements during elective and intrapartum caesarean section. Standard recommended doses are higher than required, with the potential for acute cardiovascular adverse effects. We recommend a small initial bolus dose of oxytocin, followed by a titrated infusion. The recommended doses of oxytocin may have to be increased in women with risk factors for uterine atony. Carbetocin at equipotent doses to oxytocin has similar actions, while avoiding the requirement for a continuous infusion after the initial dose and reducing the need for additional uterotonics. As with oxytocin, carbetocin dose requirements are higher for intrapartum caesarean sections. A second-line agent should be considered early if oxytocin/carbetocin fails to produce good uterine tone. Women with cardiac disease may be very sensitive to the adverse effects of oxytocin and other uterotonics, and their management needs to be individualised.

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What other guideline statements are available on this topic?

There are currently no other guidelines or recommendations that deal specifically with uterotonic management at caesarean section. There are existing guidelines that cover: management of caesarean section; management of uterine tone at vaginal delivery; and management of postpartum haemorrhage.

Why was this consensus statement developed?

There is wide variation in the use of uterotonics at caesarean section including: choice of drug (first-line and second-line uterotonics); timing of administration; dose; route; speed of administration; and maintenance regimen. Practice is based largely on tradition, rather than robust scientific data. There is evidence that adverse effects of oxytocin may be reduced by alterations in dose and rate of administration, without compromising effectiveness.

How does this consensus statement differ from other available guidelines?

This statement recommends: doses of oxytocin for routine elective caesarean section that are lower than in other guidelines; higher oxytocin doses in women at increased risk of postpartum haemorrhage; use of second-line uterotonics; use of carbetocin as an alternative to oxytocin; and a strategy for the use of uterotonics in resource-limited environments.

Why does this statement differ from existing guidelines?

This statement reviews the recent scientific literature to provide evidence-based recommendations, and focuses on the optimal dose, route and rate of administration of uterotonics during caesarean section.

Recommendations for clinical practice

1. Oxytocin or carbetocin are recommended for routine administration immediately after delivery of the fetus during caesarean section to prevent postpartum haemorrhage.
2. Oxytocin and carbetocin dose requirements for intrapartum caesarean section are several times greater than that for low-risk elective caesarean section, and therefore a universal dose for all cases is not appropriate.
3. Oxytocin has significant adverse effects when given as a rapid high-dose bolus. It should therefore be given slowly to reduce these effects. A small initial dose followed by a controlled infusion is the optimum approach. Suggested doses are given in Box 1.
4. Research is lacking on oxytocin dose requirements for women having elective caesarean section who are at high risk of uterine atony and haemorrhage. In this situation, it may be appropriate to follow the dose regimen for intrapartum caesarean section.
5. Infusion regimens for oxytocin are highly variable, but large total oxytocin doses should be avoided to minimise the antidiuretic effect. Administration of a concentrated solution using a syringe pump may be required for women who require fluid restriction.
6. Carbetocin is a longer-acting analogue of oxytocin, with a similar mechanism of action and adverse effects profile. The increased duration of action of carbetocin compared with oxytocin eliminates the requirement for an infusion after the initial dose. It may, therefore, become the preferred first-line drug, rather than oxytocin.
7. If oxytocin/carbetocin do not provide adequate uterine tone, a second-line drug (ergot alkaloids or a prostaglandin) should be considered early. Administration of a second-line agent should be guided by the clinical context and presence of contra-indications, and follow local hospital policies and availability.
8. In resource-constrained settings, where controlled intravenous (i.v.) infusions are not readily available, the intramuscular (i.m.) route can be considered for sustained duration of drug action.
9. Women with significant cardiac disease may be very sensitive to the adverse effects of oxytocin and other uterotonics, and their management needs to be individualised.
10. As accidental administration of uterotonic drugs before delivery of the fetus may result in a catastrophic outcome, extreme care must be taken to ensure that pre-prepared syringes or solutions are not confused with other drugs that may be given during this period.

Box 1 Suggested dose regimens for uterotonic administration at low-risk elective caesarean section, and caesarean section in labouring women. N.B. take account of national drug license restrictions. See text for further information.

First-line drugs

Oxytocin

Elective caesarean section	Intrapartum caesarean section
Bolus 1 IU oxytocin; start oxytocin infusion at 2.5–7.5 $IU.h^{-1}$ (0.04–0.125 $IU.min^{-1}$).	3 IU oxytocin over ≥ 30 s; start oxytocin infusion at 7.5–15 $IU.h^{-1}$ (0.125–0.25 $IU.min^{-1}$).
If required after 2 min, give a further dose of 3 IU over ≥ 30 s.	
Consider second-line agent early in the event of failure of this regimen to produce sustained uterine tone.	
Review the patient's clinical condition before discontinuing the infusion; this will usually be between 2 h and 4 h after commencement.	

Alternative – carbetocin

Elective caesarean section	Intrapartum caesarean section
100 μg over ≥ 30 s.	100 μg over ≥ 30 s.
Smaller doses (as low as 20 μg) may be sufficient; in this case, doses can be repeated if required, up to 100 μg.	Do not exceed 100 μg – if required move to second-line drug.
Do not exceed 100 μg – if required move to second-line drug.	

Second-line drugs

These drugs should be considered for both prophylaxis and treatment of postpartum haemorrhage.

Consider early use in the event of failure of first-line drugs to produce sustained uterine tone.

Depending on local availability, the following drugs can be used:

1. Ergometrine (ergonovine) 200–500 μg/methylergometrine (methylergonovine) 200 μg: i.m., or slow i.v. in exceptional circumstances; may be repeated after 2 h.
2. Misoprostol 400–600 μg: sublingual, rectal, vaginal, oral; repeat after 15 min if required, maximum dose 800 μg.
3. Carboprost 250 μg: i.m. or intramyometrial (contraindicated i.v.); up to every 15 min if required, maximum eight doses.
4. Sulprostone 500 μg: i.v. at 100 $\mu g.h^{-1}$; maximum dose 1500 μg.

Consider early use of adjunctive medication to counter adverse effects, for example, antiemetics.

Further uterotonic administration (third-line drugs) should be considered within a multimodal postpartum haemorrhage regimen (pharmacology/haematology and antifibrinolysis/surgery/interventional radiology).

Introduction

Management of uterine tone after delivery involves giving a prophylactic uterotonic, and the use of controlled cord traction to facilitate delivery of the placenta and minimise blood loss. This is usually accomplished with a single drug – however, supplementary drugs are sometimes required.

Oxytocin, or its analogue carbetocin, is the first-line drug. Oxytocin has its primary effect on oxytocin receptors in the uterus; it also has adverse effects that are mediated by oxytocin receptors as well as other receptors in the cardiovascular system [1]. Adverse effects such as ST segment depression, hypotension and tachycardia are well recognised, and have been implicated as a contributory cause of maternal death [2, 3]. Ergot derivatives and prostaglandins, the second-line drugs, also have significant cardiovascular and other adverse effects.

International guidelines on uterotonic use during caesarean section are variable (Table 1) [4–13]. Most guidelines make a single recommendation for uterotonic use, and do not discuss the use of additional agents in the presence of persistent uterine atony.

A number of surveys of uterotonic administration by obstetricians and anaesthetists show huge variation in practice, including mode of administration (bolus vs. continuous infusion), frequency (routine vs. selective use) and single vs. repeat bolus administration (Table 2) [14–20].

It is clear that focused recommendations on uterotonic use at caesarean section, including prophylaxis and escalating treatments, are required [19].

Definitions

Drugs that induce uterine contraction as their primary pharmacological action may be referred to as uterotonics, and we will use this term hereafter. 'Oxytocic' is sometimes used with the same meaning, but as some drugs that cause uterine contraction are not derived from oxytocin, this could lead to confusion and so is not used here. We use the following terms:

First-line drug – a uterotonic drug used prophylactically after delivery, as part of an active management strategy to establish uterine tone and prevent primary postpartum haemorrhage.

Second-line drug – a uterotonic drug used after the first-line drug when: a woman is considered at higher risk of postpartum haemorrhage; the obstetrician's subjective judgement is that uterine tone is inadequate after the first-line agent or intra-operative blood loss is greater than would be anticipated (potential postpartum haemorrhage).

Postpartum haemorrhage is usually defined as blood loss > 500 ml, with major/severe haemorrhage being blood loss > 1000 ml; these thresholds have been recommended as standard outcome measures for reporting postpartum haemorrhage trials [21].

Oxytocin

Oxytocin exerts its effects through binding to G protein-coupled receptors. Oxytocin receptors are widely expressed throughout the body, including the myometrium and endometrium, cardiovascular system and central nervous system. Towards the end of pregnancy there is a dramatic increase in oxytocin receptors in the uterus. The uterotonic effects of oxytocin are mediated in two ways: firstly, by stimulation of the receptor leading to a direct contractile effect in the myometrium; and secondly, by stimulating production of prostaglandin PGF2α in the endometrium [22].

Similarly to other G protein-coupled receptors, oxytocin receptors undergo rapid homologous desensitisation [22]. This phenomenon has been shown to occur both in vitro and in vivo, and has significant clinical implications, including the uterine response to subsequent administration of oxytocin. It is, therefore, important to distinguish between two clinical situations; elective or scheduled caesarean section (oxytocin-naive) and intrapartum (emergency) caesarean, where the woman was in labour and/or having exogenous oxytocin infusion (oxytocin-exposed), as there are major differences both in circulating hormone levels as well as acute changes in receptor-sensitivity in these circumstances.

Elective caesarean section

Most studies evaluating uterotonic use in elective caesarean section have been conducted in uncomplicated low-risk women as this aids consistent responses.

Bolus

Two studies have examined the optimal dose for elective caesarean section in healthy uncomplicated pregnancies at low risk for uterine atony. Carvalho et al. [23], using an up–down sequential allocation design, showed that a dose of 0.35 (95%CI 0.2–0.5) IU was effective in obtaining adequate uterine tone in 90% of women at 3 min after administration. Once adequate uterine tone was achieved and the study was completed, an infusion of 2.4 $IU.h^{-1}$ was started as a maintenance regimen for 6 h.

Table 1 Recommendations for the use of uterotonic agents during caesarean section from official bodies.

	First-line drug for PPH prophylaxis	Second-line drug for PPH prophylaxis
Royal College of Obstetricians and Gynaecologists, UK, 2016 [4]	Oxytocin 5 IU by slow i.v.	Ergometrine–oxytocin may be used in the absence of hypertension in women at increased risk of haemorrhage as it reduces the risk of minor PPH (500–1000 ml). For women at increased risk of haemorrhage, it is possible that a combination of preventative measures might be superior to oxytocin alone to prevent PPH.
American College of Obstetricians and Gynecologists Practice Bulletin number 183 Postpartum Hemorrhage, 2017 [5]	Prophylactic oxytocin by dilute i.v. infusion (bolus dose of 10 IU) or intramuscular injection (10 IU).	Not discussed. Guidance moves to discussing management of established haemorrhage recommending that uterotonic agents are the first-line treatment for PPH secondary to uterine atony but the specific agent selected is at the healthcare provider's discretion.
Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2017 [6]	Active management of the third stage of labour (use of prophylactic oxytocics and assisting delivery of the placenta) should be practised as this reduces the risk of PPH and the need for blood transfusion. No agent/dose recommended	Not discussed. Guidance moves to discussing management of established haemorrhage recommending that uterotonic agents are the first-line treatment for PPH secondary to uterine atony.
Society of Obstetrics and Gynaecologists of Canada, 2009 [7]	Carbetocin 100 μg given as an i.v. bolus over 1 min	Second line recommendation of oxytocin infusion or ergonovine (ergometrine) would appear to apply to vaginal delivery only. No specific second-line recommendation for caesarean section
French College of Obstetricians and Gynaecologists in collaboration with French Society of Anaesthesiology and Intensive Care, 2015 [8]	Oxytocin 5–10 units i.v. except for women with overt cardiovascular risks when the injection must last at least 5 min to limit its haemodynamic effects. Routine maintenance 10 IU.h^{-1}, review after 2 h. The guideline states that carbetocin reduces the risk of PPH but in the absence of non-inferiority trial oxytocin remains the drug of choice for prophylaxis.	Not discussed Guidance moves to discussing PPH management algorithms for PPH following vaginal delivery, occurring during caesarean section and delayed PPH after caesarean section. An oxytocin infusion and sulprostone are recommended.
Deutsche Gesellschaft für Gynäkologie und Geburtshilfe, 2016 [9]	Oxytocin 3–5 IU slowly i.v.	Carbetocin 100 μg slowly i.v.
World Health Organization Recommendations for the prevention and treatment of postpartum haemorrhage, 2018 [10]	The use of an effective uterotonic for the prevention of PPH during the third stage of labour is recommended for all births. To effectively prevent PPH, only one of the following uterotonics should be used: • oxytocin (10 IU, i.m./i.v.) • carbetocin (100 μg, i.m. /i.v.) • misoprostol (either 400 μg or 600 μg, oral) • ergometrine/methylergometrine (200 μg, i.m./ i.v.) • oxytocin and ergometrine fixed-dose combination (5 IU/ 500 μg, i.m.) In settings where multiple uterotonic options are available, oxytocin (10 IU, i.m./i.v.) is the recommended uterotonic agent for the prevention of PPH.	Not discussed.

(continued)

Table 1 (*continued*)

	First-line drug for PPH prophylaxis	Second-line drug for PPH prophylaxis
FIGO (International Federation of Gynecology and Obstetrics) Safe Motherhood and Newborn Health Committee Prevention and treatment of postpartum hemorrhage in low-resource settings [11]	Within 1 min of delivery of the infant, palpate the abdomen to rule out the presence of an additional infant(s) and give oxytocin 10 IU intramuscularly. Oxytocin is preferred over other uterotonic drugs because it is effective 2–3 min after injection, has minimal adverse effects, and can be used in all women. If oxytocin is not available, other uterotonics can be used, such as: ergometrine or methylergometrine 0.2 mg intramuscular; syntometrine (a combination of oxytocin 5 IU and ergometrine 0.5 mg per ampoule intramuscular [10]); or misoprostol 600 μg orally.	Not discussed. Guidance moves to discussing management of established haemorrhage and recommends that, for management of PPH, oxytocin should be preferred over ergometrine or methylergometrine alone, a fixed dose combination of ergometrine and oxytocin, carbetocin, and/or prostaglandins such as misoprostol. If oxytocin is not available, or if the bleeding does not respond to oxytocin or ergometrine, an oxytocin–ergometrine fixed dose combination, carbetocin, or misoprostol should be offered as second-line treatment. If these second-line treatments are not available, or if the bleeding does not respond to the second-line treatment, a prostaglandin such as carboprost tromethamine should be offered, if available.
National Institute Of Health and Care Excellence (NICE), UK [12]	Oxytocin 5 IU by slow i.v. injection	Not discussed
Association of Women's Health, Obstetric and Neonatal Nurses, USA [13]	Administer i.v. oxytocin by providing a bolus dose followed by a total minimum infusion time of 4 h after birth. For women who have had caesarean births, continuation beyond 4 h is recommended. Rate and duration should be titrated according to uterine tone and bleeding.	Not discussed

PPH, postpartum haemorrhage; i.m., intramuscular.

Butwick et al. [24] performed a dose–response study of oxytocin doses between 0 IU and 5 IU. They found a ceiling effect, with limited benefit for doses > 0.5 IU to obtain adequate uterine tone after 2 min. Interestingly, adequate uterine tone, without need for additional oxytocin, was obtained in 73% of women in the 0 IU group. There were no differences in adverse effects between 0.5 IU and 1 IU; however, adverse effects increased with doses > 1 IU.

Infusion

It is common practice in North America to administer oxytocin by a rapid, often unregulated infusion, for example, 30 IU oxytocin in 500 ml crystalloid solution, rather than by a bolus [25]. These high-rate infusions, designed to initiate uterine tone, must therefore be distinguished from lower rate infusions for maintenance of tone.

Two dose-finding studies have determined the optimal calibrated oxytocin infusion rates to initiate adequate uterine tone. George et al. found that the ED_{90} (95%CI) of an oxytocin infusion to obtain satisfactory uterine tone, at an initial assessment 4 min after delivery, was 0.29 (0.15–0.43) $IU.min^{-1}$ (17.4 (9.0–25.8) $IU.h^{-1}$) [26]. Lavoie et al., using comparable methodology, found a very similar ED_{90} of 0.27 (0.21–0.32) $IU.min^{-1}$ (16.2 (13.1–19.3) $IU.h^{-1}$) [27]. Given that the end-point of adequate uterine tone was assessed at 4 min, the total dose administered at this point was approximately 1 IU, consistent with the studies using a single bolus dose. Both of these studies switched to a standard fixed oxytocin infusion rate, one at the end of surgery and the other after 1 h.

A study that investigated change in haemoglobin after delivery found that oxytocin 40 $IU.h^{-1}$ in 500 ml, infused over 30 min, was as effective as 60 or 80 $IU.h^{-1}$ over the same infusion time [28].

Oxytocin has only weak antidiuretic activity when the infusion rate is < 2.7 $IU.h^{-1}$ [29], suggesting that the infusion rate should be restricted, if possible, to minimise the effects of oxytocin on renal haemodynamics and water and electrolyte excretion.

Bolus plus infusion

Duffield et al. compared infusions of 2.5 $IU.h^{-1}$ and 15 $IU.h^{-1}$ after an initial 1 IU oxytocin bolus. They found no evidence of

Table 2 Surveys of clinical practice of uterotonic use at caesarean section (CS).

Name, Country	Population	Respondent/ response rate	First dose of oxytocin				Infusion protocol after initial bolus			Second-line protocol
			5 IU		10 IU					
Bolton, UK [14]	Lead obstetric anaesthetists	179 (75%)	10% (5% rapid, 5% slow)		87% (50% rapid, 50% slow)		Not discussed			Not discussed
Bolton, UK [14]	Lead obstetric anaesthetists	198 (77%)	82% (20% rapid, 62% slow)		15% (23% rapid, 77% slow)		Not discussed			Not discussed
Wedisinghe, UK [15]	Lead obstetricians and lead obstetric anaesthetists	365 (84%)	90% slow		12.1% slow		Routine – 20% Selective – 80% 30 IU over 4 h – 43% 40 IU over 4 h – 53%			Oxytocin 5 IU bolus – 17%
Marcus, Germany [16]	Chairs of anaesthetic departments	346 (48%)	1–3 IU 52%	5–9 IU 21%	10 IU 12%	12–40 IU 1.8%	3–9 IU – 17% 10 IU – 50% 12–20 IU – 15% 23–40 IU – 6.4%			
Mockler, Australia and New Zealand [17]	Obstetric fellows (members of Royal Australian and New Zealand College of Obstetricians and Gynaecologists)	700 (45%)	32%		67%		68 different infusion regimens; most common is 40 IU in 1 l over 4 h			Ergometrine – 26% Syntometrine (oxytocin 5 IU + ergometrine 500 μg) – 20% Oxytocin bolus –19% Commencement of oxytocin infusion –21% (no details about routes of administration or dosage)
Sheehan, UK and Ireland [18]	Lead obstetricians and lead anaesthetists	391 (82%)	UK – 12% Ireland – 9.0%		UK – 89% Ireland – 85%		Routine: UK – 19% Ireland – 36% Selective: UK – 80% Ireland – 67% 30 IU over 4 h: UK – 43% Ireland – 3.0% 40 IU over 4 h: UK – 40% Ireland – 43%			Not discussed
West, UK [19]	Lead obstetric anaesthetists (OAA members)	150 (73%)		<5 IU	5 IU	> 5 IU	Routine – 24% Selective – 76% 7–10 IU.h^{-1} over 4 h – 86%			Identical oxytocin bolus repeated –90% Smaller repeat oxytocin bolus –8.7% Larger repeat oxytocin bolus – 0.7%
			Elective	5.4%	95%	0%				
			Emergency	4.7%	95%	0%				
Orbach-Zinger, Israel [20]	Obstetricians and anaesthetists; six university hospitals; all grades	390 (90%)		1 IU	5 IU	10 IU		10 IU in 1 l Ringer's lactate	20 IU in 1 l Ringer's lactate	Second line – usually increased bolus of oxytocin or increase rate Third-line-methylergometrine
			First CS	4.3%	31%	11%	First CS	32%	21%	
			Repeat CS	4.1%	27%	17%	Repeat CS	30%	21%	

CS, caesarean section.

improved tone or reduced blood loss, despite a six-fold difference in infusion rate, suggesting that very low doses are required by infusion after an initial bolus. Furthermore, this study corroborates the efficacy of a low-dose bolus of 1 IU to initiate appropriate uterine contraction [30].

Kovacheva et al. [25] found that a 3 IU oxytocin bolus over 15 s, repeated twice if necessary and followed by a maintenance infusion of 3 IU per hour, was as effective as their standard regimen of a 'wide open' (full flow rate, uncalibrated) infusion of 30 IU in 500 ml. There were no differences in uterine tone, haemodynamic changes or other adverse effects, or the requirement for alternative uterotonic agents.

The reported benefits of oxytocin infusion after bolus compared with bolus only include: reduced estimated blood loss; less postpartum haemorrhage; fewer blood

transfusions; and a lower requirement for additional uterotonics [31, 32].

The optimal duration of oxytocin infusion after initiation of tone is unknown. A convenient time to review this is at the point of discharge from the postoperative recovery area.

Intrapartum caesarean section

Bolus

The ED_{90} for adequate uterine tone in women undergoing caesarean section for failure to progress (arrested labour) was found to be 2.99 (95%CI 2.3–3.7) IU [33], nine times the dose found at elective caesarean section using similar methodology [23]. This is likely to result from oxytocin receptor desensitisation, as the women received oxytocin infusion during labour for a mean (SD) of 9.8 (6.3) h before caesarean section. As with this group's earlier study, a maintenance infusion of 2.4 $IU.h^{-1}$ was used for 6 h after achieving adequate uterine contraction and completion of the study [23].

Infusion

Lavoie et al. [27] studied labouring women having caesarean section, using identical methods to those in women having elective caesarean section. They determined the ED_{90} (95%CI) for oxytocin infusion to obtain satisfactory tone at 4 min after delivery, in women who had had an oxytocin infusion during labour, as 0.74 (0.56–0.93) $IU.min^{-1}$ (44.2 (33.8–55.6) $IU.h^{-1}$), almost three times higher than women not in labour. The oxytocin dose at the 4-min assessment mark was approximately 3 IU. Additionally, 34% of women having caesarean section during labour required supplementary uterotonic agents, compared with 8% women having elective caesarean section [27].

Munn et al. [34] found that additional uterotonics were required in 39% vs. 19% (RR 2.1), when using 10 IU given over 30 min compared with 80 IU oxytocin, respectively.

A retrospective chart review found that women who had a caesarean section after receiving oxytocin during labour required a higher postpartum oxytocin infusion rate than those who did not, with an adjusted OR of 1.94 (95% CI 1.19–3.15; p = 0.008]) [35]. The former group was also more likely to require additional uterotonic agents.

Bolus plus infusion

A trial in a mixed study population of elective and intrapartum caesarean section in women with ≥ 1 risk factors for uterine atony (overdistended uterus; oxytocin infusion during labour; chorioamnionitis; clinical history; placenta praevia; high parity) showed no significant differences in the need for additional uterotonic drugs in the first 24 h when comparing 5 IU oxytocin administered over 30 s, with a placebo bolus followed by an infusion of 40 IU oxytocin in 500 ml over 30 min. There were small differences in uterine tone immediately after delivery of the placenta, which was no longer apparent 5 min later [36].

Adverse effects

Haemodynamic effects

The haemodynamic effects of oxytocin are related to the following: the dose administered; rate of administration; the presence of comorbidities, such as pre-eclampsia or cardiac disease; the volume status of the patient; and whether repeated doses are administered. Recent studies of oxytocin administration during caesarean section under regional anaesthesia, using non- or minimally invasive monitors employing beat-by-beat pulse wave form or transthoracic bioimpedance technology, have shown peripheral vasodilatation, hypotension, and increased cardiac output, mediated by an increase in heart rate and stroke volume after oxytocin administration [37].

The effects of oxytocin on the pulmonary and systemic circulation have been measured in a study using pulmonary artery catheterisation. A 10 IU bolus of oxytocin was followed by a 40% decrease in femoral artery pressure, and a 59% and 40% decrease in systemic and pulmonary vascular resistance, respectively, after 30 s. Heart rate increased by 31% and stroke volume by 17%, and cardiac output increased by 54%. At 150 s after injection, pulmonary artery and pulmonary wedge pressure had increased by 33% and 35%, respectively. However, all women in this study had undergone general anaesthesia, which limits comparability with women having regional anaesthesia [38].

Slow administration of oxytocin results in less cardiovascular effects. A 5 IU dose administered as an infusion over 5 min was associated with a 5 mmHg reduction in mean arterial pressure and a 10 $beats.min^{-1}$ increase in heart rate, compared with a 27 mmHg decrease and a 17 $beats.min^{-1}$ increase seen after the same 5 IU dose given as a bolus [39]. Repeated doses of oxytocin are associated with an attenuated cardiovascular effect, possibly from receptor desensitisation [37].

Co-administration of 80 μg phenylephrine with 2.5 IU oxytocin, given over 30 s, has been shown to obtund but not prevent the decrease in systemic vascular resistance and increase in heart rate and cardiac output [40]. In another study, administration of 50 μg phenylephrine before a 3 IU

oxytocin dose given over 15 s did not prevent hypotension and tachycardia [41].

In women with pre-eclampsia, similar transient haemodynamic effects were seen after a 2.5 IU oxytocin bolus when compared with healthy women [42], although in another study the response to a 5 IU bolus was less consistent, with five out of 18 women experiencing a decrease in cardiac output due to inability to increase stroke volume [43].

A further observational study of 0.1–0.5 IU oxytocin doses in women with various cardiac conditions, including aortic stenosis, peripartum cardiomyopathy and congenital heart disease, showed considerable, although transient, decreases in blood pressure and increases in cardiac output [44].

A negative inotropic effect of oxytocin has been found in the atrium of dogs [45]. In human atrial myocytes, this effect has been attributed to the preservative chlorobutanol rather than to oxytocin itself [46].

The significance of ST depression at caesarean section, and its relationship with myocardial injury, has been debated. ST segment changes at caesarean section occur in up to 25–47% of women [47, 48]. Chest pain in association with ST depression has an incidence of 5–33% [47–49]. Suggested precipitating factors include hypotension, tachycardia, venous air embolism and ephedrine-induced tachycardia; although there are conflicting opinions and no definitive evidence on causation, oxytocin is likely to play a contributory role [47–50].

One study found that 11 out of 26 women developed intra-operative ST segment changes. Only two women had an increase in cardiac troponin I, indicating myocardial ischaemia, and these women showed ST segment changes only in the postoperative period [50]. Although the mechanism is unclear, the evidence for myocardial injury in a minority of women at caesarean section is likely to be significant, as troponin I is not elevated after vaginal delivery [51].

Oxytocin use can cause ST depression independent of anaesthesia. A bolus dose of 10 IU oxytocin produced transient ST depression in approximately 50% of women undergoing caesarean section with spinal anaesthesia, but this effect was also seen in a similar percentage of non-pregnant and non-anaesthetised women given the same dose [52]. This adverse cardiovascular effect of oxytocin is dose-dependent. A randomised trial found that ST depression occurred in 8% of women after a 5 IU oxytocin bolus vs. 22% after 10 IU (53). This was related to more severe hypotension in the latter group. However, troponin elevation occurred with a similar incidence of 4% after both doses, showing that there is no tight linkage between ST depression and myocardial injury. Interestingly, one third of episodes of ST depression were either before or after more than 3 min following oxytocin administration, furthering the suggestion that oxytocin is only one of several factors producing ST depression [53].

The haemodynamic effects of oxytocin are also dependent on the mode of administration. ST depression occurred in three out of 40 women when 3 IU oxytocin was given over 15 s, but in none when it was infused over five min [54].

Several reports, during both caesarean section and vaginal delivery, indicate that rapid administration of bolus oxytocin to women who are hypovolaemic may cause extreme haemodynamic instability or collapse. A 10 IU bolus of oxytocin was the precipitating cause of death in two women, one of whom had a high spinal block and was also hypovolaemic, and the other who had pulmonary hypertension [2]. An oxytocin bolus was thought to have contributed to five maternal deaths in the South African Confidential Enquiries into Maternal Deaths between 2005 and 2010 [3].

Other adverse effects

Oxytocin can cause water retention and subsequent hyponatraemia, as the drug has a structural analogy with antidiuretic hormone (ADH; vasopressin), and therefore activates the ADH receptor [55, 56]. Oxytocin can cause nausea and vomiting; vomiting occurred in 15% of women after a 5 IU bolus followed by a 10 IU infusion over 24 h [57]. This adverse effect is dose related, as nausea occurred in 5% vs. 33%, and vomiting in 2.5% vs. 15% of women after 2 IU or 5 IU oxytocin, respectively [58]. Butwick et al. did not find a relationship with nausea using doses up to 5 IU, although the study was not powered to study this outcome [24]. Other adverse effects observed with oxytocin include: feelings of warmth; palpitations; flushing; nasal congestion; xerostomia; metallic taste; headache [59]; shivering; and pruritus [60].

Breastfeeding

The use of oxytocin during labour has been implicated in reduced rates of breastfeeding. Potential mechanisms by which exogenous oxytocin might affect breastfeeding include down-regulation of oxytocin receptors in the mother [61], as well as transplacental passage [62]. There are no relevant data on the effect of oxytocin vs. other uterotonics on breastfeeding following caesarean section; however, reassuring data come from a prospective

randomised controlled trial evaluating active management of the third stage of labour including oxytocin vs. physiological management, which found no differences in breastfeeding rates at hospital discharge [63].

Carbetocin

Carbetocin is a synthetic oxytocin analogue, with a chemical structure of 1-de-amino-1-carba-2-tyrosine (0-methyl) oxytocin. This makes it less susceptible to metabolism by deamination and disulphidase cleavage [64]. It has a plasma half-life of approximately 40 min following i.v. injection, 4–10 times longer than that of oxytocin. In addition, carbetocin has a higher lipophilicity than oxytocin, which alters its tissue distribution and is responsible for an increased half-life in the receptor compartment [65].

Carbetocin has a similar affinity for the oxytocin receptor as oxytocin. Despite a similar affinity, its potency in animal models is about one-tenth that of oxytocin on a mole per mole basis [65]; the decreased potency of carbetocin compared with oxytocin has been confirmed in in-vitro studies using human myometrial strips [66]. Oxytocin pre-treatment of term pregnant human myometrium attenuated contractions produced by carbetocin [66], which was similar to the effects shown with further administration of oxytocin [66].

The recommended dose of carbetocin is 100 μg, which is equivalent to 10 μg (5 IU) of oxytocin. Several dose-finding studies have suggested that the ED_{90} of carbetocin at elective caesarean section in low-risk women is as low as 14.8 μg [67–69], less than one-fifth the currently recommended dose. A recent non-inferiority randomised study compared a dose of carbetocin of 20 μg with 100 μg. The study did not demonstrate that 20 μg was non-inferior to 100 μg for the primary outcome of intensity of uterine tone at 2 min (i.e. the lower dose might be inferior). However, all the secondary outcomes of uterine tone at 5 min, use of additional uterotonics in the first 24 h and blood loss were similar in the two groups [70]. There is some indication, therefore, that a lower than standard dose of carbetocin is acceptable during elective caesarean section, but these results need to be confirmed in future studies.

As has been observed with oxytocin, the ED_{90} of carbetocin for intrapartum caesarean section is higher than for elective caesarean section at 121 μg, which is likely to be from oxytocin receptor desensitisation [71]. The intrapartum-to-elective dose ratio is similar to that for oxytocin. This may have implications for clinical practice, as some women having intrapartum caesarean section may not respond to the standard ampoule dose of 100 μg. However, doses higher than 100 μg have been associated with cardiovascular complications such as tachycardia and intra-operative arrhythmias, and cannot currently be recommended [71]. As for oxytocin, it is expected that women having intrapartum caesarean section will require more frequent uterotonic supplementation with a second-line uterotonic after carbetocin than at elective caesarean section.

A Cochrane review published in 2012 included 11 studies on 2635 women comparing a 100-μg bolus dose of carbetocin, by various routes of administration, with other uterotonic agents, following either vaginal delivery or caesarean section [72]. Where oxytocin was the comparator, the dose used varied considerably between studies. Pooled data from the review showed that for women who underwent caesarean section, carbetocin resulted in a lower risk of severe postpartum haemorrhage (measured or clinically estimated blood loss 1000 ml or more; risk ratio (RR) 0.55, 95%CI 0.31–0.95), additional therapeutic uterotonics (RR 0.62, 95%CI 0.44–0.88) and need for uterine massage following delivery (RR 0.54, 95%CI 0.37–0.79), compared with oxytocin [72].

Despite exhibiting a more favourable adverse effect profile than oxytocin, carbetocin is associated with cardiovascular adverse effects. It can cause hypotension, nausea, vomiting, ST depression, arrhythmias, flushing and abdominal pain, as observed with oxytocin [71, 73, 74]. Studies comparing the cardiovascular effects of standard 100 μg doses of carbetocin and 5 IU oxytocin during caesarean section under spinal anaesthesia have shown essentially indistinguishable hemodynamic effects for the two drugs [59, 75].

Although pre-eclampsia and eclampsia are included as contra-indications in the manufacturer's license, one randomised controlled trial found that the use of carbetocin in patients with severe pre-eclampsia had no major adverse haemodynamic effect [76].

Only very small amounts of carbetocin cross from plasma to breast milk [77]. This is not of clinical concern, as carbetocin is rapidly degraded in the infant's gastro-intestinal tract.

In a simulated model of 1500 caesarean sections over a 12-month period, using clinical data from a meta-analysis and pricing data from the UK, carbetocin was found to have a 91.5% probability of being associated with a lower incidence of postpartum haemorrhage (reducing cases with blood loss > 500 ml from 88% to 58%) and savings of

> £27,000 compared with oxytocin [78]. A similar study from Malaysia found an even higher clinical impact of carbetocin, with a prevention of 54 cases of postpartum haemorrhage and 52 transfusions per 1500 caesarean sections annually, when compared with oxytocin [79].

There are concerns about a loss in potency of oxytocin during storage at high temperatures [80], which were not corroborated by other authors [81]. The manufacturer states that carbetocin can be kept for 1 month at temperatures up to 60 °C, 3 months at 50 °C, 6 months at 40 °C and 3 years at 30 °C [82].

Other uterotonic agents

Second-line uterotonics include ergot alkaloids and prostaglandins.

Ergometrine (ergonovine) and methylergometrine (methylergonovine) are ergot alkaloids that increase the uterine muscle tone by sustained uterine contraction via nonspecific activation of adrenergic, dopaminergic and 5-HT receptors. They have a plasma half-life of 30–120 min. The most frequent adverse effects include hypertension, nausea and vomiting [83, 84]. Ergot alkaloids may produce peripheral vasoconstriction that leads to elevated systemic arterial pressure and central venous pressure. It is relatively contra-indicated in women with pre-eclampsia and hypertension as exaggerated hypertensive effects may be seen. They have been associated with coronary artery spasm, causing chest pain and palpitations. Besides nausea and vomiting, other side-effects include diarrhoea, headache, abdominal pain and dyspnoea.

The UK license for ergometrine is for doses up to 500 μg; however, in a number of countries lower doses of 200–250 μg are recommended.

Prostaglandins are bio-active lipids derived from arachidonic acid, which act as paracrine or autocrine agents that bind to different G protein-coupled receptors. Some prostaglandins stimulate myometrial contraction via activation of FP, EP1, EP3 and TP receptors. Misoprostol is a prostaglandin-E1 analogue, which is licensed for the prevention and treatment of gastric ulcers. It is in unlicensed use worldwide as a uterotonic agent [85]. It is absorbed 9–15 min after sublingual, oral, vaginal or rectal use. The half-life is 20–40 min. The most prominent side-effect of misoprostol is hyperpyrexia [86].

Carboprost, a synthetic PGF2α analogue, and sulprostone, a synthetic PGE2 analogue, are also used during treatment of postpartum haemorrhage, but are not used for prophylactic treatment during caesarean section due to significant adverse effects. Carboprost can cause significant bronchospasm, even in patients without asthma [87]. Other effects include hypertension, diarrhoea, nausea, vomiting, flushing, hyperpyrexia and myalgia [88]. Sulprostone may cause fever, diarrhoea and painful uterine contraction [89]. There are reports of cardiac or respiratory side-effects, including cardiac arrest, when sulprostone was administered during haemorrhagic shock, combined with dinoprost, or off-license as a continuous i.v. infusion [90].

A recent Cochrane network meta-analysis, including 196 clinical trials with 135,559 women, studied all combinations of prophylactic uterotonic drugs, after both vaginal and caesarean deliveries. There were no trials that investigated ergot alkaloids or prostaglandins, alone or in combination with oxytocin, vs. placebo as a first-line prophylactic treatment at caesarean section. Prophylactic use of carbetocin alone during caesarean section did not decrease the rate of postpartum haemorrhage compared with placebo [83]. In a sub-group analysis evaluating the risk of blood loss ≥ 500 ml at caesarean section, only the combination of an infusion of 20 IU oxytocin plus sublingual misoprostol 400 μg was superior to oxytocin alone (RR 0.69, 95%CI 0.51–0.92; pairwise analysis). For major postpartum haemorrhage (blood loss ≥ 1000 ml), there was no evidence for differences between any agent and oxytocin alone [83]. The lack of directly comparable studies makes it difficult to draw definite conclusions.

A propensity score-matched secondary analysis of registry data investigated the effect of second-line uterotonics given for persistent uterine atony after failed oxytocin prophylaxis [91]. They analysed a registry with 1335 women who had undergone caesarean section and who had received carboprost or methylergometrine. The risk of haemorrhage-related morbidity (red blood cell transfusion; need for additional surgical interventions to control bleeding) was significantly increased in the carboprost group, even after correction for confounders (relative risk 1.7; 95%CI 1.2–2.6).

There is some evidence that an escalating strategy for the management of increased bleeding after vaginal delivery can reduce postpartum haemorrhage rates [92], and this may also be applicable at caesarean section [93].

Resource-limited settings

Drugs that are reserved as second-line agents in high-resource settings may be appropriate as first-line agents when oxytocin is not available. Potential resource problems include lack of the following: drug; reliable refrigeration facilities for non-thermostable formulations; infusion pumps; and disposables.

The limitations of resource-poor environments place even greater emphasis on careful risk-benefit decisions regarding the use of uterotonic agents. The adverse haemodynamic effects of oxytocin are likely to be more pronounced in hypovolaemic women, and therefore slow and judicious administration of the drug is even more important than in routine cases.

The i.v. route is preferable to i.m. administration for the initial bolus of oxytocin [94]. However, if a postoperative infusion of oxytocin is desired, but cannot be administered reliably due to problems with staffing or equipment, i.m. administration is an alternative. A suggested protocol is syntometrine (5 IU oxytocin with 500 μg ergometrine; or if contra-indicated 10 IU oxytocin) repeated after 4 h [3].

Safety considerations

Uterotonic agents given accidentally before delivery can have catastrophic consequences for the neonate. A UK survey of drug errors in obstetric anaesthesia reported that three of 70 involved administration of oxytocin before delivery [95]. Epidural administration of oxytocin has also been described, which, although undesirable, did not lead to uterine tonic contraction [96].

Strategies that have been described to minimise the risk of drug errors include: carefully reading the ampoule label; coloured labels for the syringe; separate trays in the workspace; pre-filled syringes; and only drawing up oxytocin when it is required [97, 98]. Other strategies used by the consensus authors to reduce error with uterotonics include: and drawing up into 1-ml tuberculin syringes; and drawing up oxytocin into 100 ml bags of saline.

Limitations of the recommendations from the consensus group

The consensus group has attempted to provide evidence-based recommendations wherever possible. However, the literature is heterogeneous and does not encompass all clinical situations. In clinical practice, the practitioner may alter doses depending on the perceived complexity of the case. In particular, there are a growing number of elective caesarean sections with multiple risk factors for poor uterine contractility. Furthermore, with a trend to performing elective caesarean sections at a later gestation in order to allow fetal lung maturation, women are more commonly presenting with uterine contractions or with ruptured membranes, and do not fit clearly into the labouring 'intrapartum' category.

Details of licensing of uterotonic drugs vary from one country to another. We have provided common dosage schedules. The practitioner will have to take account of local regulations when incorporating these consensus recommendations into their practice.

Besides licensing, there are differences in availability, and pharmacological formulation, of uterotonic drugs in different countries. This applies especially to the second-line agents, and therefore we have not provided didactic recommendations for administration of different agents, but merely the most common dosing schedules.

Future directions

Standardised protocols to study the effectiveness of uterotonic drugs at caesarean section should be developed.

Large studies with clinically important end-points, such as accurately measured blood loss [99], are required [21].

With an increasing prevalence of women at high risk of uterine atony having caesarean section, information to guide optimal administration of oxytocin and other uterotonics in this group of patients is highly desirable.

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