

OBSTETRICS

— the drug options

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The second article in our special feature discusses the drugs used around the time of labour, covering those used in routine practice as well as those used to manage certain high risk groups

Although the majority of births are relatively straightforward, therapeutic interventions during labour are common. These interventions include thromboprophylaxis, anti-infectives for prophylaxis and treatment of puerperal infections, therapies to induce or augment labour, and analgesia.

THROMBOPROPHYLAXIS

Pregnancy can increase the risk of venous thromboembolism (VTE) tenfold¹ and VTE remains a major cause of maternal mortality in the United Kingdom.² Women need to be assessed for thromboprophylaxis at regular intervals throughout their pregnancy. A proportion of these women will require antenatal thromboprophylaxis (Panel 1),¹ and others will only need prophylaxis post delivery (Panel 2).¹

Both unfractionated heparin and low molecular weight heparin (LMWH) have been used for thromboprophylaxis in pregnancy. LMWHs are now recommended in preference to unfractionated heparin because there are more safety data.¹ LMWHs have the advantage of reduced side effects and, in most situations, once daily administration. However, care has to be taken with the timing of doses in relation to epidural and spinal analgesia to minimise the risk of spinal haematomas. Spinal and epidural analgesia should not be used for 10-12 hours after LMWH has been administered. LMWH should not be given for two hours after spinal or epidural analgesia or catheter removal.

The dose of LMWH will depend on the risk of thromboembolism. Women at high risk will receive therapeutic doses calculated on the early pregnancy body weight, where-

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Panel 1: Risk factors that merit consideration for antenatal thromboprophylaxis

- Antithrombin deficiency
- Long-term warfarin
- Antiphospholipid syndrome with previous VTE or recurrent miscarriage
- Previous pregnancy or oral contraceptive related VTE or previous idiopathic VTE
- Protein C or S deficiency
- Thrombophilia and personal history of VTE

as those at medium risk will receive a fixed dose. Where the risk of thromboembolism is considered to be low or heparin is contraindicated, mechanical methods (eg, compression hosiery) are used and, in some situations, aspirin.

PUERPERAL INFECTION

The early identification and treatment of infection in the puerperal period is essential to prevent death due to genital tract sepsis.² The most common organism responsible for serious and life-threatening infection is beta-haemolytic *Streptococcus pyogenes* (Lancefield Group A). The most appropriate antibiotics are piperacillin/tazobactam plus an aminoglycoside. The dosing of aminoglycosides can be difficult during the puerperium as a result of changes in drug handling. The use of once daily gentamicin has not been validated in pregnancy. Therapeutic drug monitoring is essential and usually a twice daily dosing regimen is necessary.

Group B streptococcal disease (GBS) is a leading cause of early onset neonatal sepsis

in developed countries. In the United States, two strategies are recommended to reduce neonatal sepsis. One is to screen women routinely for GBS between 35-37 weeks gestation. The other involves assessment of clinical risk factors (risk-based approach) to identify women for prophylaxis. In both approaches, antibiotics are administered during labour if GBS is identified. A recent study found that routine screening prevented more cases of early-onset disease than the risk-based approach.³

In Britain, there are insufficient data on the prevalence of early-onset GBS to support either strategy. The Public Health Laboratory Service GBS working group has issued interim recommendations for best practice⁴ (Panel 3). The antibiotic regimen for GBS prophylaxis consists of a *stat* dose of 3g benzylpenicillin intravenously at the start of labour and then 1.5g every four hours until the delivery of the baby. Instructions

Panel 2: Risk factors that merit consideration for postpartum thromboprophylaxis

- Over 35 years of age
- Caesarean section
- Operative vaginal delivery
- Obesity (BMI >30kg/m²)
- Parity 4
- Labour >12 hours
- Gross varicose veins
- Pre-eclampsia
- Lower limb paralysis
- Immobilisation (>4 days' bed rest)
- Current infection
- Extended pelvic or abdominal surgery
- Major current medical conditions
- Thrombophilia or personal history of VTE

for preparation should be available because benzylpenicillin is supplied in 600mg vials. Women allergic to penicillin are prescribed clindamycin 900mg intravenously every eight hours. Antibiotics should also be given to the neonate in certain situations.⁴

Antibiotic prophylaxis should be used for women undergoing caesarean section to reduce infectious complications such as fever, wound infection, endometritis, bacteraemia, urinary tract infection and pelvic abscess.⁵ A single dose of a second generation cephalosporin, such as cefuroxime, is administered immediately after the cord is cut to avoid exposing the baby to the antibiotic.

The use of antiretrovirals for the prevention of mother-to-child transmission of HIV became common practice in the developed world during the early 1990s. Oral zidovudine starting at 14 to 34 weeks gestation and an infusion during labour or caesarean section was recommended in HIV-positive women, followed by zidovudine for six weeks for the baby. This regimen was found to reduce the incidence of vertical transmission from 25 per cent to 8 per cent.⁶ An alternative regimen that reduced transmission rate by 50 per cent⁷ was a single dose of intrapartum nevirapine, and one dose to the baby, soon after birth.

The more aggressive treatment of HIV infection during pregnancy using triple therapy has reduced even further the inci-

dence of mother-to-child transmission. It is recommended that women should continue with their current antiretroviral therapy, with the exception of efavirenz, where there are concerns about teratogenicity. If the triple therapy includes zidovudine, an infusion should be administered during labour or caesarean section. The British HIV Association guidelines advise on how to manage different scenarios.⁸

Until the publication of the ORACLE I⁹ and ORACLE II¹⁰ trials there was considerable uncertainty as to whether antibiotics should be given in preterm prelabour rupture of membranes (pPROM) or spontaneous preterm labour with intact membranes (SPL-IM). For pPROM it was shown that a 10-day course, or until delivery, of erythromycin was associated with a range of health benefits for the neonate. The use of co-amoxiclav could not be recommended because of an association with necrotising enterocolitis.⁹ There was no evidence to recommend routine antibiotics in SPL-IM where there was no evidence of clinical infection.¹⁰

— OXYTOCIN DURING LABOUR

In modern obstetrics, intravenous oxytocin use is common.¹¹ Routine indications include induction and augmentation of labour, prevention of postpartum haemor-

rhage in third stage labour and management of postpartum haemorrhage. The drug's use in induction and augmentation of labour presents the most challenge because there is little consensus about the optimal dosage.¹²⁻¹⁴

Induction is used to start labour before it has occurred spontaneously. It involves cervical priming and induction of contractions. This intervention is carried out predominantly for "post term" pregnancies — usually term plus 10 days. There is continued debate about the merit of this practice but it stems from concerns that by this stage in pregnancy the placenta may not function adequately.^{13,15} Other situations where induction may be carried out include diabetes, iso-immunisation, hypertension, pre-eclampsia, twin pregnancy, malposition or malpresentation of the fetus, pelvic abnormality and haemorrhage in late pregnancy. In some units, induction is carried out at the woman's request.

The most commonly used regimen involves the use of dinoprostone (prostaglandin E₂) vaginal gel 1mg or 2mg (depending on the parity) for priming. The dose can be repeated after four to six hours if required. Dinoprostone can also be given orally and as pessaries but these formulations are rarely used in practice because response may not be as predictable as with the gel. Side effects include nausea, vomiting, diar-

Panel 3: Intrapartum antibiotic prophylaxis for GBS infection or other situations⁴

Give GBS antibiotic regimen

- GBS infection in a previous baby
- GBS found incidentally in the vagina at any time during pregnancy
- GBS found incidentally in the urine at any time during pregnancy

Give broad spectrum antibiotics (including cover for GBS)

- Chorioamnionitis diagnosed or suspected
- Pre-term prolonged rupture of membranes

Consider giving antibiotics

- Labour is preterm
- Prolonged rupture of membranes in labour
- Fever in labour

rhoea, cramps and painful contractions. Flushing, shivering, pyrexia (not to be interpreted as a sign of infection) and headache can also occur. Close observation of mother and fetus is essential to detect any signs of uterine over-reaction, especially in multiparous women, or fetal distress. Use of dinoprostone is contraindicated in placenta praevia (where the placenta is wholly or partially within the lower part of the uterus), fetal distress and severe asthma.

Another prostaglandin analogue that is increasingly being used for induction is misoprostol, given orally or vaginally. This is an unlicensed use of the drug. Vaginal misoprostol (25–100µg) was found to be more effective than oxytocin or dinoprostone for inducing vaginal deliveries within 24 hours.¹⁶ However, there are still concerns about the introduction of this treatment into routine care because its optimal dosage and the true prevalence of uterine hyperstimulation are not known.

Once the cervix is sufficiently dilated, oxytocin infusion can be initiated, with the dose titrated to stimulate uterine contractions. Success is highly dependent on the state of the cervix. If the membranes are intact, routine amniotomy (rupture of membranes) can be carried out at the time of starting oxytocin infusion. This process also has the advantage of enabling examination of the amniotic fluid. Use of oxytocin is not advised if no amniotic fluid can be seen or if meconium is present.

Oxytocin is given by continuous infusion by an infusion pump. Clear instructions for the preparation and administration of a low volume infusion need to be in place. Dosage titration is vital, in response to regular monitoring of mother and fetus. In view of the serious dose-related side effects, a system to detect pump failure is advisable. Adverse effects associated with oxytocin include hypertension, arrhythmias and pulmonary oedema. Oxytocin has an antidiuretic effect. At higher dosages, urinary output can fall

and result in water intoxication, which may present as confusion, nausea, convulsions and, rarely, coma.

Hyperstimulation is of concern because it can result in uterine rupture, haemorrhage, amniotic fluid embolism and fetal distress. If hyperstimulation occurs, oxytocin administration must be stopped. Inhaled (some units use nebulised) salbutamol may reverse this effect. If there is no response, ritodrine infusion and, more recently, oral nifedipine have been used. Maternal oxygen administration will be needed if there is fetal bradycardia.

Some women have less than optimal uterine activity (dysfunctional labour) during either spontaneous or induced labour. Oxytocin, again by continuous infusion, is commonly used to speed up or augment labour.¹⁴ This is different from its use to induce labour.^{12,13,15}

Some units routinely use oxytocin to shorten labour, a practice referred to as “active management of labour”.¹¹ Starting doses vary from 0.5–6.0mU/min. At intervals of 20–60 minutes, the dose is generally increased.^{11,14} Using a low dose produces fewer side effects, but this has to be balanced against the short labour that results from using a high dose.

Oxytocin can also be used in third stage labour (the period between the birth of the baby and delivery of the placenta) to reduce the risk of postpartum haemorrhage. Syntometrine (oxytocin 5 units/ergometrine 0.5mg) has been the product of choice but use of oxytocin alone has become increasingly popular, driven by women’s preference. It is also used in preference to Syntometrine in known cases of hypertension. There is little difference in efficacy between IM Syntometrine and IV oxytocin 10 units^{17,18} except that the former results in a higher incidence of nausea, vomiting, headache and hypertension. Intravenous oxytocin (the licensed route of administration) appears superior to the intramuscular route and this may be due to the rapid onset of action.

— ACID ASPIRATION SYNDROME

With the increasing caesarean section rate, acid aspiration syndrome continues to be an issue. It is a rare yet serious complication of obstetric anaesthesia, especially in emergency caesarean section. The severity and extent of pulmonary damage appears to be highest when the gastric pH is less than 2.5 and volume of aspirate is more than 25ml.

Many units minimise this risk by alkalisation of the stomach content using a non-particulate antacid (sodium citrate) and by reduction of the volume of gastric acid secretion using ranitidine.¹⁹ Comparable efficacy may be achieved by using ranitidine alone.²⁰ Intravenous ranitidine is used for optimal cover in emergency situations. Due to the cardiovascular problems that have sometimes been associated with intravenous cimetidine, many hospitals have chosen to use ranitidine.

— SEVERE PRE-ECLAMPSIA

Pre-eclampsia is a multiorgan disease that is a common cause of maternal and fetal morbidity and mortality. It usually presents with hypertension and proteinuria.²¹ Progression from the mild to severe stage can occur rapidly in some women. Haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, eclampsia (seizures) and end stage renal failure are rare and serious complications.

Prompt delivery is the only certain way to avoid further damage. Several therapeutic interventions²¹⁻²⁴ are used to manage the condition until delivery is possible, depending on the gestation and severity.

Associated hypertension is usually managed conservatively. It is essential to lower blood pressure slowly to avoid marked hypotension and further organ damage. Practice is variable in choice of antihypertensives. Many units start by a trial of oral

(not sublingual) nifedipine. There are no reports of reduction in the utero-placental blood flow and fetal compromise. Of most concern are associated headache, dizziness and reflex tachycardia. If response is poor, antihypertensives given by small IV boluses followed by infusion are introduced. Hydralazine or labetalol are commonly used.^{23,24}

Labetalol has a better side effect profile, rapid onset of action (10 minutes), and synergy with nifedipine but it should not be used in women with asthma and it can result in marked fetal bradycardia, fetal hypoglycaemia, and chronic use may result in reduced fetal growth.

Hydralazine has a delayed onset of effect (20-30 minutes) — this often leads to a too rapid dose increase which can result in profound hypotension and tachycardia. The drug is metabolised by acetylation and therefore its effect can be variable depending on the acetylase status. A rare lupus-like syndrome has

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been reported after prolonged oral use. Common side effects include headaches, flushing and palpitations.

Eclamptic seizures are considered a medical emergency. Management has to include clear and readily available instructions on preparation of the required medicines. One of the medicines which now has worldwide approval for its benefits is magnesium sulphate infusion.²²

The recent MAGPIE trial confirmed that magnesium sulphate can halve the risk of eclampsia and placental abruption in women with severe pre-eclampsia.²¹ It is administered as a loading dose of 4g followed by 1g/hour infusion. Although serious side effects are rare, there is a risk of respiratory and cardiovascular arrest. There should be a system for monitoring of side effects and serum magnesium concentration. It is essential to avoid NSAID use until coagulation defects have resolved, because of the additive risk of renal and haematological problems.

— PAIN MANAGEMENT

There are several options available to women for the management of pain during labour. As part of the preparation for childbirth, the midwife will normally discuss these options, which include non-pharmacological methods such as transcutaneous electric nerve stimulation (TENS). The form of pain relief that the woman actually receives may vary considerably from what was planned because the degree of pain may be more or less than expected or there may be complications during labour that influence the choice.

The most widely used analgesia during labour is a 50 per cent mixture of nitrous oxide and oxygen (Entonox, Equanox). It is self-administered using a demand valve to prevent excessive sedation. For maximal effect it should be inspired at the onset of a contraction before pain is experienced. Cylinders should not be exposed to temper-

atures below 0C or separation of the gases may occur. It is important to store them for 24 hours above 10C before use or to invert them three times before use.

Pethidine is the most widely used systemic opioid for pain management in labour. However, there are concerns about its effectiveness and side effects, such as neonatal sedation, respiratory depression and reduced sucking reflex.

Other opioids used include morphine, diamorphine, meptazinol and pentazocine. These all have a similar range of side effects — but to differing degrees — including nausea, vomiting, drowsiness, hypotension, altered uterine contractions and respiratory depression in the newborn. A recent review of intramuscular opioids for maternal pain relief in labour²⁵ found that there is not enough evidence to evaluate their comparative efficacy and safety.

Patient controlled analgesia (PCA) has been used but does not work as well during

Panel 4: Some advantages and disadvantages of lumbar epidural analgesia

Advantages

- Woman awake and co-operative
- Low incidence of complications
- Provides analgesia or anaesthesia for vaginal or caesarean section
- Beneficial in prolonged labour
- Reduced exposure of infant to opioid

Disadvantages

- Possibility of poor perineal analgesia
- Presence of areas where analgesia is insufficient
- Delayed onset of action
- Technically difficult to perform
- Risk of intravascular injection
- Accidental dural puncture leading to post-dural puncture headache or convulsions
- Risk of hypotension
- Itch if opioid used

labour as in the post-operative situation, because of the different nature of the pain during labour. Pethidine and fentanyl are the opioids most commonly used for PCA.

Regional analgesia is based on the premise that labour pain is transmitted through lower thoracic, lumbar and sacral nerve roots. The choice of technique is dependent on duration and onset of action, the degree of analgesia/anaesthesia required and the stage of labour. Epidural or spinal analgesia, or a combination of both, are used to block pain from the uterus and birth canal. Techniques include paracervical block, pudendal block and caudal analgesia. A paracervical epidural block may be used when a prolonged first stage of labour is expected. A pudendal block may be used for an episiotomy and low forceps delivery and spinal analgesia just before a caesarean section.

Epidural analgesia is highly effective in reducing the pain of labour.²⁶ A solution of local anaesthetic or opioid, or a combination of both, is injected via a catheter placed into the epidural space. The anaesthetist sites the catheter and gives the first dose; top-up doses are then given by the midwife or an infusion can be used. The technique of patient controlled epidural bolus on a background of a continuous infusion has been used. Bupivacaine or lidocaine are the most common local anaesthetics used for epidural analgesia. The addition of an opioid such as fentanyl reduces the dose of local anaesthetic and associated motor blockade. Panel 4 lists advantages and disadvantages of epidural analgesia. In spinal analgesia, a solution of

local anaesthetic, opioid or a combination of the two is injected into the subarachnoid space using a fine spinal needle. Panel 5 lists advantages and disadvantages of spinal analgesia.

Hypotension can occur in up to 50 per cent of patients receiving epidural or spinal analgesia. Placing a woman on her side to avoid aortocaval compression can reduce the incidence. In addition, foot elevation and a rapid administration of 250ml of IV fluids (usually sodium chloride 0.9 per cent or Hartmann's solution) followed by administration of IV ephedrine or phenylephrine in incremental doses can be administered until stability is restored. Infiltration of the perineum with a local anaesthetic is performed when an episiotomy is needed or suturing is required to mend perineal tears. Lidocaine 1 per cent (10–20ml) is most commonly used and a midwife performs the technique.

Post-delivery analgesia is important, especially after a caesarean section or instrumental delivery. Regular dosing of analgesics using a combination of paracetamol, a NSAID (when not contraindicated) and an opioid is often required. These should be started before the effects of the regional analgesia have worn off. Pain score should be assessed regularly and dosages and timing of analgesics tailored to requirements.

CONCLUSION

Provision of pharmaceutical care during labour is challenging, because there is a need to balance the needs of both the mother and the baby. It is also necessary to allow for the changes in maternal drug handling that occur during pregnancy.

Panel 5: Some advantages and disadvantages of spinal analgesia

Advantages

- Woman awake and co-operative
- Use of lower dosage of local anaesthetic or opioid than with epidural analgesia
- Excellent analgesia
- Onset of action rapid
- Satisfactory muscle relaxation
- Uterine activity unaffected

Disadvantages

- Technically difficult to perform
- Risk of post-dural puncture headache
- Risk of hypotension
- Itch if opioid used
- Poor motor function leading to inability of mother to push

The confidential enquiry into maternal deaths² highlighted high risk groups and emphasised the need for guideline-led care to direct best practice. The specialty requires regular pharmaceutical input within the multidisciplinary team to deliver optimal care.

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