Guidelines for the diagnosis and management of acute myeloid leukaemia in pregnancy

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Summary of recommendations

- Pregnant women should be managed by a multidisciplinary team that includes haematologists, obstetricians, neonatologists and anaesthetists (Grade 1C)
- As for non-pregnant patients, acute myeloid leukaemia (AML) should be diagnosed using the World Health Organization (WHO) classification (Grade 1A)
- Women diagnosed with AML in pregnancy should be treated without delay (Grade 1B)
- When the diagnosis of AML is made in the first trimester, a successful pregnancy outcome is unlikely and spontaneous pregnancy loss in this situation carries considerable risks for the mother. The reasons for and against elective termination should be discussed with the patient (Grade 2C)
- In the case of presentation beyond 32 weeks gestation, it may be reasonable to deliver the foetus prior to commencement of chemotherapy (Grade 2C)
- Between 24 and 32 weeks, risks of foetal chemotherapy exposure must be balanced against risks of prematurity following elective delivery at that stage of gestation (Grade 1C)
- The risk-benefit ratio must be carefully considered before using any drugs in pregnancy (Grade 1C)
- Where AML induction chemotherapy is delivered, a standard daunorubicin, cytarabine 3 + 10 schedule should be used (Grade 1B)
- Chemotherapy should be dosed according to actual body weight and adjustments made for weight changes during treatment (Grade 1C)
- Quinolones, tetracyclines and sulphonamide use should be avoided in pregnancy (Grade 1B)
- Amphotericin B or lipid derivatives are the antifungal of choice in pregnancy (Grade 2C)
- Cytomegalovirus (CMV)-negative blood products should be administered during pregnancy regardless of CMV serostatus (Grade 1B)
- A course of corticosteroids should be considered if delivery is anticipated between 24 and 35 weeks gestation, given over a 48-h period during the week prior to delivery (Grade 1A)
- Use of magnesium sulphate should be considered in the 24 h prior to delivery if this is before 30 weeks gestation (Grade 1A)
- Where possible, delivery should be planned for a time when the woman is at least 3 weeks post-chemotherapy to minimize risk of neonatal myelosuppression (Grade 1C)
- Planned delivery is easier to manage than spontaneous labour; induction of labour is usually advised (Grade 2C)
- Epidural analgesia should be avoided in a woman who is significantly thrombocytopenic (platelet count <80 × 10^9/l) and/or neutropenic (white blood cell count <1 × 10^9/l): (Grade 1C)
- Elective caesarean section should only be recommended for obstetric indications (Grade 2C)
- Antibiotics should be administered during and after premature rupture of membranes and delivery (Grade 1C)

Keywords: acute myeloid leukaemia, pregnancy, chemotherapy, foetus, teratogenic risk.

Scope

Methodology

Literature review. The guideline group was selected to be representative of UK-based medical practitioners with
expertise in the management of acute myeloid leukaemia (AML). Recommendations are based on review of the literature using MEDLINE and PUBMED up to December 2013 under the heading: 'acute myeloid leukaemia', 'pregnancy' and 'chemotherapy'.

Recommendation grading. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria are specified in the BCSH guidance pack (http://www.bcshguidelines.com/BCSH_PROCESS/EVIDENCE_LEVELS_ANDGRADES_OF_RECOMMENDATION/43_GRADE.html) and the GRADE working group website (http://www.gradeworkinggroup.org).

Writing Group Membership and Review Arrangements. SA, GJ, DC, NR and CC are consultant haematologists. PM is a consultant obstetrician and NE a consultant neonatologist. The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haematology Task Force of the British Committee for Standards in Haematology (BCSH). The guideline was then reviewed by the haematology oncology sounding board of the British Society for Haematology (BSH). This comprises 50 or more members of the BSH who have reviewed this guidance and commented on its content and applicability in the UK setting. It has also been reviewed by the UK AML National Cancer Research Network (NCRN) working group and by representatives of Leukaemia Care but they do not necessarily approve or endorse the contents.

Background

This guidance has been developed because the BCSH haematology oncology taskforce have decided that a degree of consensus or uniformity is likely to be beneficial to patient care despite a low quality evidence base. As a result, whilst the literature has been reviewed, many of the recommendations outlined are, by necessity, derived from expert opinion rather than rigorous trials. This is reflected in the grade of evidence assigned to recommendations. The guidance may not be appropriate to every patient and individual patient circumstances may dictate an alternative approach. The management of acute promyelocytic leukaemia in pregnancy has been addressed separately within recent European guidelines (Sanz et al., 2009) and will not be further discussed within the current guidance.

Introduction

Leukaemia during pregnancy is uncommon, occurring in approximately one in 75 000 to one in 100 000 pregnancies. Acute leukaemia accounts for the vast majority of these presentations with acute lymphoblastic leukaemia representing approximately one-third and acute myeloblastic leukaemia (AML) two-thirds of cases (Hurley et al, 2005).

Diagnosis of malignancy during pregnancy poses a huge challenge to the pregnant patient, her family and the medical team. The fact that optimal anti-leukaemic treatment may be associated with adverse foetal outcomes including malformation or death raises a complicated maternal-foetal conflict. The dilemma faced by women in pregnancy at gestations where delivery is not an option is very real and patients need sufficient time and considerable support in making their decisions.

Diagnosis

Diagnosis of leukaemia in pregnancy is more challenging than in non-pregnant individuals because anaemia, which can be multifactorial, is relatively common in pregnancy. Initial suspicion of a more serious cause for anaemia is usually triggered by an abnormal blood count and blood film appearances. Whilst both thrombocytopenia and anaemia are relatively common findings in pregnancy, neutropenia is more rare and merits further investigation or close monitoring. The presence of circulating blasts in a blood film suggests a diagnosis of haematological malignancy and is an indication for bone marrow biopsy. The investigations listed in Table I should be undertaken before a marrow biopsy is performed.

Diagnostic criteria

The diagnostic criteria for AML are the same in a pregnant patient as in non-pregnant women. These criteria are defined in the World Health Organization (WHO) classification of the myeloid neoplasms (Vardiman et al, 2009). Where a diagnosis of leukaemia is suspected, care must be taken to ensure that marrow samples are directed for immunophenotypic, cytogenetic and molecular analysis to allow accurate sub-typing and understanding of prognostic features.

Management at diagnosis

Patients diagnosed with AML during pregnancy should be managed jointly by consultant haematologists, obstetricians, anaesthetists and neonatologists. Consideration should be given to the health of both mother and baby and the informed wishes of the mother. The woman should be fully informed about the diagnosis, treatment of the disease and possible complications during pregnancy.

Table I. Essential investigations.

<table>
<thead>
<tr>
<th>Test</th>
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<tbody>
<tr>
<td>Full blood count and blood film examination</td>
</tr>
<tr>
<td>Vitamin B12, folate and ferritin measurement</td>
</tr>
<tr>
<td>Coagulation screen</td>
</tr>
<tr>
<td>Renal and liver function tests</td>
</tr>
</tbody>
</table>
Treatment delays may compromise maternal outcome without improving the outcome for the foetus (Greenlund et al., 2001). Without treatment, maternal death can occur within weeks or months (Cardonick & Iacobucci, 2004). In addition, leukaemia in a pregnant woman carries an increased risk of miscarriage, foetal growth restriction and perinatal mortality (Reynoso et al., 1987; Cardonick & Iacobucci, 2004; Cheghoum et al., 2005). The earlier in gestation the diagnosis of leukaemia is made, the higher the incidence of spontaneous miscarriage, premature labour and foetal growth restriction. Suspected causes of foetal death include maternal anaemia, disseminated intravascular coagulation and leukaemic cells affecting blood flow, nutrient exchange and oxygen delivery in the intervillous spaces of the placenta (Cardonick & Iacobucci, 2004). Delaying treatment would therefore have an adverse outcome for both mother and baby and, unless the pregnancy is advanced, treatment should be commenced as early as possible. Involvement of the multidisciplinary team in discussing options with the woman, whilst taking account of her stage of pregnancy, is essential.

Issues of management in the first trimester
The earlier in pregnancy that a diagnosis of AML is made, the higher the risks to that pregnancy. The patient should be counselled regarding risks to the pregnancy, risks of continuing with the pregnancy and the importance of timely chemotherapy for the AML.

Spontaneous abortion before 12 weeks gestation is common, occurring in 20% of confirmed viable pregnancies in healthy women. Rates are even higher in women with AML (Doll et al., 1988; Cardonick & Iacobucci, 2004). Owing to the high risk of spontaneous miscarriage, significant foetal malformation and foetal death as a result of AML, its complications and its treatment, it is reasonable to consider elective termination of pregnancy when a diagnosis is made in the first trimester (Grade 2C). Elective termination of pregnancy is considered to be safer for the mother, than taking the risk of a spontaneous miscarriage given that the platelet count and coagulation parameters can be more tightly controlled in the elective situation. Medical termination of pregnancy is preferable to surgical intervention but both can be managed if there is a tight control of haemostasis.

Issues of management in the second and third trimesters
Chemotherapy delivered during the second and third trimesters rarely causes congenital malformation, but does increase the risk of late miscarriage, prematurity, foetal growth restriction, neonatal neutropenia and sepsis (Doll et al., 1988; Ebert et al., 1997; Cardonick & Iacobucci, 2004). However, successful chemotherapy treatments during the second and third trimesters in a host of different malignant conditions, including acute leukaemia, are well documented and delivery of a non-malformed, healthy baby is still the most likely outcome. The relatively low risk of chemotherapy to the foetus should be emphasized, whilst acknowledging that the long-term effects, if any, on the infant remain uncertain. The woman should also be informed that delaying chemotherapy would carry a significant risk to her health and her baby, and would therefore not be advisable. The advice, in second and third trimesters, would therefore usually be to continue with the pregnancy and start chemotherapy. Particular consideration needs to be given, however, to balancing the risks of foetal prematurity and risks of foetal chemotherapy exposure later in the third trimester.

Survival following delivery at or beyond 28 weeks gestation of an otherwise ‘well’ foetus are >90% in most large centres, but even higher (>95%) if the baby is delivered at or beyond 32 weeks gestation. It may be considered reasonable to deliver the baby before commencing chemotherapy if a woman presents at 30–32 weeks gestation. However, although short-term morbidity rates are also low at these gestations, there is a linear relationship between decreasing rates of minor neurocognitive impairment as gestation increases towards 36 weeks. Chemotherapy should not be given after 36 weeks’ gestation because spontaneous delivery is increasingly likely to occur before the bone marrow has recovered. The implications of starting chemotherapy in the third trimester and the risks to the woman of delaying chemotherapy to gain advantage for the baby need to be discussed with the mother.

At all gestations below 36 weeks the woman should have an opportunity to discuss the mortality and morbidity rates, specific to the stage of pregnancy, associated with premature delivery with an experienced neonatologist. Between 24 and 28 weeks the foetal risks related to prematurity are high and, since chemotherapy appears to carry a low risk to the foetus, delivery would not usually be advised and treatment should not be delayed. Survival rates are higher and disability rates lower for gestations beyond 28 weeks and therefore the risks of prematurity need to be weighed against the risk of chemotherapy. Overall, the diagnosis of AML beyond the first trimester does not usually require termination or very early delivery. Decisions to delay delivery by a week or two, to confer an advantage for babies at critical gestations, for example 26 weeks, should only be taken within the multidisciplinary team setting.

Decisions need to be made by the haematologists, obstetricians and neonatologists in conjunction with the mother as to the relative risks of early induction of labour and the likelihood of foetal survival, in order that treatment plans can be individualized.

Recommendations
- Pregnant women should be managed by a multidisciplinary team that includes haematologists, obstetricians, neonatologists and anaesthetists (Grade 1C)
- As for non-pregnant patients, AML should be diagnosed using the WHO classification (Grade 1A)
Guideline

- Women diagnosed with AML in pregnancy should be treated without delay after full and frank discussion with the patient (Grade 1B)
- When the diagnosis of AML is made in the first trimester, a successful pregnancy outcome is unlikely and spontaneous pregnancy loss in this situation carries considerable risks for the mother. The reasons for and against elective termination should be discussed with the patient (Grade 2C)
- In the second trimester (13–24 weeks), consideration should be given to commencing induction chemotherapy and allowing the pregnancy to proceed, after careful discussion with patient and obstetric specialists (Grade 2C)
- Between 24 and 32 weeks risks of foetal chemotherapy exposure must be balanced against risks of prematurity following elective delivery at that stage of gestation (Grade 1C)
- When presentation is beyond 32 weeks gestation, it may be reasonable to deliver the foetus prior to commencement of chemotherapy (Grade 2C)
- Chemotherapy should be avoided at or beyond 36 weeks gestation and elective delivery is recommended (Grade 1C)

Chemotherapy and complications

When pregnancy is not advanced enough to consider early induction of labour, combination chemotherapy with daunorubicin and cytarabine as per standard AML protocols should be offered (daunorubicin 60 mg/m²/d by intravenous infusion on days one, three and five and cytarabine 100 mg/m² 12-hourly by intravenous push on days one to ten inclusive). Whilst this is a regimen considered standard in the UK, internationally other anthracycline-based regimens are favoured and there are no data to support the use of one specific regimen over another. There are also no data, however, to support the use of higher dose daunorubicin (90 mg/m² on days 1, 3, 5) in this patient group and this approach is not recommended.

In most series, pregnant women have been dosed on their actual body weight with dose adjustments for weight gain during pregnancy (Cardonick & Iacobucci, 2004). This seems reasonable given that the increase in blood volume consequent upon pregnancy and the increase rate of renal drug clearance may act to reduce the area under the curve for drug bioavailability. The general side effects and risks of chemotherapy in a pregnant woman being treated for AML are, in large part, similar to those risks in a non-pregnant individual. These include the risk of sepsis, but of course the potential for teratogenicity is of specific relevance and often at the forefront of the patient’s mind.

Teratogenic risk

The risk of teratogenesis following cancer treatment appears to be lower than commonly estimated from the available animal data. Therapeutic doses used in humans are often lower than the minimum teratogenic dose applied in animals. Animal data will clearly only apply clinically if the teratogenic dose is that which is used in practice (Yaffe & Briggs, 2003). First trimester exposure to chemotherapy has been associated with 10–20% risk of major malformation (Weisz et al, 2004). This risk was found to be lower with a single chemotherapy agent compared to a combination regimen (Doll et al, 1988). A summary of data is presented in Table II.

Impact of anthracyclines

Most foetal malformations observed after anthracycline treatment seem to occur during the first trimester, especially with exposure between 2 and 8 weeks gestation. In general, daunorubicin or doxorubicin should be used in preference to idarubicin, as the latter is more lipophilic, favouring more placental transfer.

It is still a matter of debate whether in utero exposure to anthracyclines in general is cardiotoxic to the foetus. However, serial prenatal sonographic assessment of foetal cardiac function might have a role in monitoring anthracycline cardiotoxicity or cardiac failure (Meyer-Wittkopf et al, 2001). Transient neonatal cardiomyopathy has been reported with idarubicin but not with doxorubicin (Meyer-Wittkopf et al, 2001; Cardonick & Iacobucci, 2004).

Impact of cytarabine

Experience of cytarabine administration during pregnancy is limited. The fact that it is an anti-metabolite, however, raises concerns regarding its safety (Shapira et al, 2008). As with the use of anthracyclines, most foetal malformations seem to occur after exposure during the first trimester. Congenital malformations, including limb malformation, have been associated with its use in the first trimester, either alone or in combination with other chemotherapeutic agents (Wagner et al, 1980; Schafer, 1981; Artlich et al, 1994; Ebert et al, 1997). Transient cytopenias, intrauterine foetal death, foetal growth restriction and neonatal death secondary to sepsis have been reported with its use during all trimesters (Cantini & Yanes, 1984; Avilés & Niz, 1988) though the risk is relatively small.

Role of hydroxycarbamide

Whilst there are few data to provide meaningful comment on the effects of hydroxycarbamide in pregnancy, it seems reasonable to avoid the use of this agent except in cases of high white cell count (greater than 100 × 10⁹/l) where the clinician believes early count control with hydroxycarbamide may improve the outcome.

Recommendations

- The risk-benefit ratio must be carefully considered before using any drugs in pregnancy (Grade 1C)
Where AML induction chemotherapy is delivered, a standard daunorubicin, cytarabine 3 + 10 schedule should be used (Grade 1B).

Chemotherapy should be dosed according to actual body weight and adjustments made for weight changes during treatment (Grade 1C).

Ongoing management during pregnancy

Women with AML who undergo chemotherapy during pregnancy should be offered regular obstetric haematological review with fortnightly ultrasound scans for growth and foetal wellbeing to detect foetal growth restriction. An anaesthetic review should be carried out in the antenatal period.

Sepsis and pregnancy

Between 2006 and 2008 sepsis rose to be the leading cause of direct maternal deaths in the UK, with deaths due to group A streptococcal infection (GAS) rising to 13 women per year. Severe sepsis with acute organ dysfunction has a mortality rate of 20–40%, which increases to 60% if septic shock develops.

Women receiving chemotherapy for AML during pregnancy are at increased risk of sepsis. Changes in the immune system in pregnancy per se also make a woman more susceptible to infection. In addition, the signs and symptoms of sepsis in pregnant women may be less typical than in the non-pregnant population and are not necessarily present in all cases. Therefore there should be vigilance for signs of infection and a high index of suspicion is necessary. If there is evidence of sepsis the woman should be managed by a senior team of haematologists, obstetricians and anaesthetists (Royal College of Obstetricians and Gynaecologists, 2012a,b).

Women are at particular risk if they have spontaneous pre-term premature rupture of membranes (PPROM). If the woman presents with PPROM and has evidence of myelosuppression, delivery should be expedited because of the significant risk of maternal sepsis, regardless of gestation. If the woman presents with PPROM at gestations 28–34 weeks gestation, but is well with no evidence of myelosuppression, delivery is still the preferred option rather than conservative management, but consideration could be given to delaying delivery by 48 h so that a course of corticosteroids can be administered. Close maternal monitoring in that situation is paramount. The benefits and risks of delaying delivery and corticosteroids at different gestations should be discussed with the mother. In particular, at gestations earlier than 28 weeks, decisions regarding the timing of delivery need to be made by the haematologists, obstetricians and neonatologists.

Table II. The outcome of pregnancies in cancer patients exposed to chemotherapy.

<table>
<thead>
<tr>
<th>Study references</th>
<th>Study period</th>
<th>Cases (n)</th>
<th>Diagnosis (n)</th>
<th>Trimester treatment commenced (n)</th>
<th>Treated with chemotherapy, n</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheghoum et al (2005)</td>
<td>1988–2003</td>
<td>37</td>
<td>AML (31) ALL (6)</td>
<td>1st (9) 2nd (10) 3rd (18)</td>
<td>37</td>
<td>15 spontaneous or therapeutic abortion 23 healthy babies (one set of twins) of whom 15 were exposed to chemotherapy</td>
</tr>
<tr>
<td>Turchi and Villasis (1988)</td>
<td>Pre-1988</td>
<td>28</td>
<td>AML (10) ALL (10) NHL (3) Solid tumours (5)</td>
<td>1st (4) 2nd (15) 3rd (9)</td>
<td>28</td>
<td>24 infants (one set of twins) of whom four had reversible pathology. Two materno-foetal deaths due to maternal malignancy</td>
</tr>
<tr>
<td>Avilés and Niz (1988)</td>
<td>1963–1981</td>
<td>23</td>
<td>AML (8) ALL (12)</td>
<td>1st (11) 2nd (5) 3rd (2)</td>
<td>23</td>
<td>Five mothers and foetuses died during induction. 20 children of 18 mothers were evaluated No foetal malformation seen</td>
</tr>
<tr>
<td>Reynoso et al (1987)</td>
<td>1968–1986</td>
<td>58</td>
<td>AML (39) ALL (19)</td>
<td></td>
<td>53</td>
<td>50 live infants 28 premature infants Four low birth weight babies, one child had a congenital anomaly and later developed neuroblastoma</td>
</tr>
<tr>
<td>Van Calsteren et al (2010)</td>
<td>1998–2008</td>
<td>180</td>
<td>46% breast cancer 18% haematological</td>
<td>Mixed gestations 62 (chemotherapy +/- radiotherapy +/- surgery)</td>
<td></td>
<td>The prevalence of preterm labour was increased (11.8%; P &lt; 0.05). Higher proportion of small-for-gestational-age children (birth weight below 10th percentile) was observed (24.2%; P &lt; 0.05). No increased incidence of congenital malformations</td>
</tr>
</tbody>
</table>

AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; NHL, non-Hodgkin lymphoma.

- Where AML induction chemotherapy is delivered, a standard daunorubicin, cytarabine 3 + 10 schedule should be used (Grade 1B).
- Chemotherapy should be dosed according to actual body weight and adjustments made for weight changes during treatment (Grade 1C).

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gists in conjunction with the mother. The risk of sepsis and the likelihood of foetal survival need to be considered in order that treatment plans can be individualized.

Supportive therapies in pregnancy

Antiemetics

Nausea and vomiting following chemotherapy is expected and may require treatment. According to the UK Teratology Information Service (UKTIS), the first choice antiemetic drugs are the antihistamines, cyclizine and promethazine (UKTIS 2010). Prochlorperazine and metoclopramide are considered second line agents because they may be associated with maternal dystonic reactions (UKTIS 2010). Ondansetron can be used in cases where first and second line antiemetic therapies have been unsuccessful (Einarson et al, 2004).

Antibiotics

Patients usually suffer severe neutropenia either at presentation or secondary to chemotherapy. The risk of infection is high, especially at induction of delivery and after membrane rupture. Antibiotics might be considered either for prophylactic or therapeutic purposes. Penicillins, erythromycin, metronidazole and cephalosporins can be safely given. Augmentin (amoxicillin and clavulanate potassium) should be avoided if possible because of an increased risk of neonatal necrotizing enterocolitis. Clindamycin, piperacillin-tazobactam (Tazocin), carbapenems and gentamicin can all be used if sepsis is suspected. Relatively limited data exist regarding the tolerability of aminoglycosides. Quinolones, tetracycline and sulphonamides should be avoided (Lynch et al, 1991).

Antifungal agents

Amphotericin B represents the systemic antifungal drug treatment with which there has been the most experience in pregnancy, with no reports of teratogenesis attributed to it. No human data are available regarding the liposomal or lipid-complex preparations, though their lipophilic nature potentially increases transplacental transfer. Animal studies have not, however, revealed evidence of teratogenicity. Ambisome, Abelcet and Amphotericin B share a US Food and Drug Administration (FDA) pregnancy category B rating (http://www.drugs.com/pregnancy-categories.html). Azoles have been demonstrated to have teratogenic effects in animal studies: posaconazole, caspofungin and itraconazole carry a category C rating and fluconazole, category D. Fluconazole is however reasonably widely used in pregnancy but at doses of less than 150 mg/d (King et al, 1998). Given the reduced nephrotoxic effects of lipid-associated drug as compared to standard amphotericin B and the reduced incidence of infusion-related toxicity, liposomal or lipid-complex amphotericin are preferred antifungal agents in the prophylactic and therapeutic setting in pregnancy.

Transfusion requirements

Cytomegalovirus (CMV)-negative blood and blood products should be administered during pregnancy irrespective of serological CMV status (to prevent congenital CMV) but are not needed during labour. In an emergency, if CMV-negative products are not available then standard leucodepleted products should be used (Department of Health 2012).

Recommendations

• Quinolones, Augmentin, tetracyclines and sulphonamides use should be avoided in pregnancy (Grade 1B)
• Amphotericin B or lipid derivatives are antifungal agents of choice in pregnancy (Grade 2C)
• CMV-negative blood products should be administered during pregnancy regardless of CMV serostatus (Grade 1B)

Preparation for and management of delivery

Planned delivery is preferable to allow timely administration of subsequent chemotherapy. Plans should be made for elective delivery as soon as foetal maturity allows but should be carefully timed and delivery should be avoided during the maternal nadir period, usually 2–3 weeks after treatment. This should allow the mother’s blood counts to be improving rather than deteriorating. The delay of delivery for 2–3 weeks after chemotherapy also facilitates foetal drug excretion via the placenta thus reducing the risk of neonatal myelosuppression. Chemotherapeutic agents administered shortly before delivery might not have been eliminated from the foetus, and drugs might therefore persist in the newborn. This is especially true for preterm babies, who have a limited ability to metabolize or excrete drugs due to the immaturity of the liver and kidneys.

Vaginal delivery is preferable to caesarean section because of the lower risks of infection and quicker recovery and therefore induction of labour is normally recommended, elective caesarean section only being advised for obstetric indications. The woman should be informed of the risks specific to caesarean section and induction of labour. Because of the advantages of a vaginal delivery, if labour has not established after a course of prostin pessaries, consideration may be given to a rest period and then starting the induction process again, although the woman should be informed that the chance of a caesarean section in this situation is higher. The risk of neonatal myelosuppression overall is low and therefore foetal scalp sampling and the use of foetal scalp electrodes, ventouse and forceps is not contraindicated.

Early involvement of the anaesthetic team, to discuss methods of pain control, is recommended. If the mother is
BCSH guidelines should be followed (Qureshi need to be given to a woman who is Rh D-negative, recent anti-D should be given subcutaneously or intravenously if an <pethidine/diamorphine, should be considered. Intramuscular injections should be avoided if the platelet count is <50 × 10^9/l.

If caesarean section is necessary in a neutropenic or thrombocytopenic woman, it should be performed under general anaesthesia rather than a regional block (epidural/spinal), again because of the risk of haematoma and infection. If a caesarean section is necessary and the woman has a platelet count <50 × 10^9/l, consultant haematological involvement is paramount so that platelets are available to cover the operation. Intravenous access should be gained and antibiotic prophylaxis should be used during and after membrane rupture and delivery.

Dexamethasone or betamethasone should be given when preterm delivery is anticipated at gestations of 24–35 weeks, to reduce the risks associated with prematurity, including respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis and cerebral palsy. Whenever possible, these drugs should be given for 48 h within the week prior to planned pre-term delivery (Royal College of Obstetricians and Gynaecologists, 2010).

Magnesium sulphate has also been demonstrated to reduce the chance of cerebral palsy and should be considered in the 24 h before delivery, if delivery is anticipated before 30 weeks (Royal College of Obstetricians and Gynaecologists, 2011).

Because of the increased risk of postpartum haemorrhage in women with AML, active management of the third stage is recommended. This includes administration of oxytocin 10 iu with the delivery of the anterior shoulder or immediately after birth of the baby and before the cord is clamped and cut. Consideration should be given to a prophylactic Syntocinon infusion (20 iu in 500 ml Hartmann/0.9% sodium chloride) over 4 h following delivery. Management of postpartum haemorrhage should otherwise be the same as in other pregnant women although consideration should be given to early recourse to carboprost, examination in theatre, balloon tamponade and a B-Lynch suture if there is continuing haemorrhage. In this situation it is imperative that there is consultant obstetric, anaesthetic and haematological involvement.

For women who are Rh D negative, standard anti-D immunoglobulin prophylaxis should be given (Qureshi et al., 2014). For patients who have a platelet count <30 × 10^9/l, anti-D should be given subcutaneously or intravenously if an appropriate product is available. If Rh D-positive platelets need to be given to a woman who is Rh D-negative, recent BCSH guidelines should be followed (Qureshi et al., 2014).

**Recommendations**

- A course of corticosteroids should be considered if delivery is anticipated between 24 and 35 weeks gestation, given over a 48 h period during the week prior to delivery (Grade 1A)
- Use of magnesium sulphate should be considered in the 24 h prior to delivery if this is before 30 weeks gestation (Grade 1A)
- Where possible, delivery should be planned for a time when the woman is at least 3 weeks post-chemotherapy to minimize risk of neonatal myelosuppression (Grade 1C)
- Planned delivery is easier to manage than spontaneous labour; induction of labour is usually advised (Grade 2C)
- Epidural analgesia should be avoided in a woman who is significantly thrombocytopenic (platelet count <80 × 10^9/l) and/or neutropenic (white blood cell count <1 × 10^9/l): (Grade 1C)
- Elective caesarean section should only be recommended for obstetric indications (Grade 2C)
- Antibiotics should be administered during and after premature rupture of membranes and delivery (Grade 1C)

**Management post-delivery**

After delivery, appropriate AML consolidation therapy should be planned to be completed as soon as feasible, taking account of remission status, prognostic risk factors and the number of cycles already given prior to delivery, in much the same way as would be done in the non-pregnant patient. It is important to try and avoid mother-baby separation as much as possible, especially over the first few postnatal days. This may dictate the optimal timing of further chemotherapy.

Pregnant women are at increased risk of venous thromboembolism, particularly in the first 10 d after delivery. A risk assessment should be made at delivery and if low molecular weight heparin is recommended this should be given 4 h after delivery, providing the platelet count is >50 × 10^9/l. This should be continued for either 10 d or 6 weeks depending on risk factors and magnitude of risk as per the Royal College of Obstetricians and Gynaecologists Guidelines (Royal College of Obstetricians and Gynaecologists, 2009).

Breastfeeding is not recommended whilst the mother is undergoing chemotherapy and until at least 2 weeks following chemotherapy completion. Local policies should be followed regarding lactation suppression, menstruation suppression and contraception.

**Neonatal follow up**

In most cases, babies will be born at, or near, term and have minimal, if any, on-going morbidity. However, the potential for adverse effects on the infant may be paramount in parents’ minds, and reassurance from the paediatric team may be important. Where cardiotoxic drugs have been administered antenatally, the use of a postnatal echocardiogram, whilst unproven, may provide reassurance for the parents.
Long-term growth problems do not appear likely, but there is potential for impact on neurocognition. Available data do not allow this risk to be well quantified, but again, many parents may find it reassuring to be offered follow-up during early infancy.

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Declarations of interest

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References


Review process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BCSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BCSH guidelines website (http://www.bcsghguidelines.com). If minor changes are required due to changes in level of evidence or significant additional evidence becomes available to support current recommendations a new version of the guideline will be issued on the BCSH website.

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Guideline