Emerging Topics and Controversies in Neonatology

Elaine M. Boyle
Jonathan Cusack
Editors

Springer

Emerging Topics and Controversies in Neonatology

Elaine M. Boyle • Jonathan Cusack
Editors

Emerging Topics and Controversies in Neonatology

Springer

Editors
Elaine M. Boyle
Department of Health Sciences
George Davies Centre for Medicine
University of Leicester
Leicester
UK

Department of Neonatology
University Hospitals of Leicester NHS Trust
Leicester
UK

Jonathan Cusack
Department of Health Sciences
George Davies Centre for Medicine
University of Leicester
Leicester
UK

Department of Neonatology
University Hospitals of Leicester NHS Trust
Leicester
UK

ISBN 978-3-030-28828-0 ISBN 978-3-030-28829-7 (eBook)
https://doi.org/10.1007/978-3-030-28829-7

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Contents

Part VI General Principles in Neonatal Care

Part I
The Fetus

Chapter 1
Pregnancy–Related Complications and Preterm Delivery

Suzanna Dunkerton and Penny C. McParland

Topics for Discussion in This Chapter

- Prematurity prevention including identifying those at high risk and interventions such as cerclage, progesterone and cervical pessaries.
- Intrapartum interventions to improve the outcome for the preterm neonate.
- Delivery at the limits of viability.
- Mode of delivery of the preterm breech baby.
- International strategy on stillbirth prevention and the increase in iatrogenic prematurity.
- Identification of fetal growth restriction.

Introduction

It is inevitable that complications of pregnancy and their obstetric management will impact on the wellbeing of the newborn infant and the care provided by neonatologists. Almost all aspects of obstetrics will be encompassed by this principle. However, in this chapter we have endeavoured to focus on the aspects of obstetrics that are undergoing the greatest change at present and also have the greatest potential to impact on the newborn baby and its wellbeing. Although many of these changes are occurring internationally, particularly in the developed world, there is inevitably a focus on changes to practice within the UK. We have therefore focussed on prematurity (both prevention and intrapartum care) and prevention of stillbirth. Although the latter would seem intuitively to be less relevant to neonatal outcomes, the consequences of the changes in practice that have occurred will impact on the care of neonates especially with a potential increase in iatrogenic prematurity.

S. Dunkerton · P. C. McParland (✉)
University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, Leicester, UK
e-mail: penelope.mcparland@uhl-tr.nhs.uk

E. M. Boyle, J. Cusack (eds.), *Emerging Topics and Controversies in Neonatology*, https://doi.org/10.1007/978-3-030-28829-7_1

Prematurity

Preterm birth is the leading cause of perinatal morbidity and mortality in developed countries [1, 2]. 7.8% of babies in the UK in 2016 were born at less than 37 weeks of gestation [3]. Approximately one third of preterm births are 'iatrogenic' (e.g. due to conditions such as pre-eclampsia or fetal growth restriction). The remaining preterm births are spontaneous and may occur because of preterm labour with intact membranes or following preterm prelabour rupture of the membranes (PPROM).

The majority of preterm births will arise in the apparently low-risk obstetric population. Whilst there are lifestyle changes that will impact on preterm birth risk for the population (such as smoking cessation and pregnancy spacing) there are as yet no reliable screening methods or interventions to offer to women in this group. Interventions are therefore usually targeted at women who are recognised as being at high risk of preterm birth [4]. Many major hospitals will have a specialist preterm birth antenatal clinic; however there is significant heterogeneity in practice between them in terms of investigations undertaken and interventions provided [5].

Risk Factors for Prematurity

Risk factors for preterm birth include previous preterm birth, multiple pregnancy, congenital uterine anomaly and maternal smoking. Previous cervical surgery for cervical intraepithelial neoplasia, such as large loop excision of the transition zone and cone biopsy, is also now established as a risk factor for preterm birth. Hopefully with the introduction of the human papillomavirus (HPV) vaccine this will reduce the number of HPV positive cervical smear changes and reduce the number of cervical loop excisions undertaken. These risk factors are routinely screened for at the antenatal booking visit to allow appropriate targeted antenatal care. More recently, previous second stage Caesarean section has been identified as a risk factor for early preterm birth and late miscarriage [6–9] and is associated with a threefold increase in risk in delivery at less than 30 weeks gestation [7]. It has been suggested that this is caused by the interruption of the sphincteric muscle fibres around the cervix either due to unintentional surgical laceration of the cervix at the time of uterine incision or by the passage of the surgeon's hand into the pelvis to disimpact the fetal head [7, 10]. This risk factor may gain greater importance in antenatal care as the rate of second stage Caesarean sections increases and that of mid-cavity and rotational instrumental deliveries decreases [11]. Novel systems such as the fetal pillow (Fig. 1.1) have been developed to aid disimpaction at second stage Caesarean section. These have been shown to reduce trauma to the fetal head and to reduce complex uterine extensions that can include the cervix [12]. However, it has yet to be demonstrated whether this will impact on the subsequent risk of prematurity in the next pregnancy.

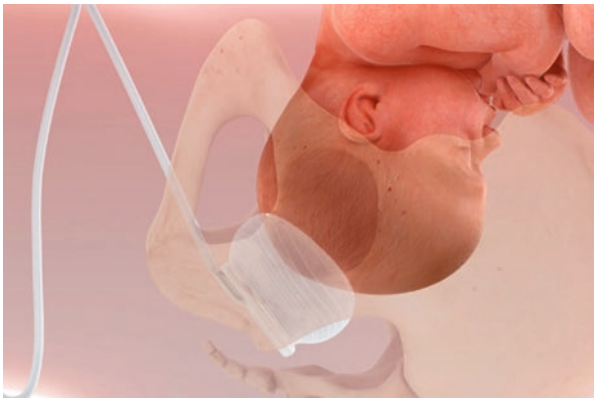


Fig. 1.1 This shows the positioning of the Fetal Pillow beneath the head of the baby, elevating the head within the maternal pelvis. (Figure from Safe Obstetric Systems, reproduced with permission)

Cervical Length Screening

Women at high risk of preterm birth are typically offered cervical length assessment by transvaginal ultrasound in the second trimester. The exact timing and frequency of these assessments is not standardised. There is an established link between a short cervical length and subsequent preterm birth, with cervical length of less than 25mm in the second trimester being associated with an increased risk of preterm birth before 35 weeks [13]. The temporal relationship between the shortened cervix and subsequent delivery is not, however, reliably predictable.

Cervical Cerclage

The purpose of assessment of cervical length in women at high risk of preterm birth is clearly to identify those in whom intervention can be offered to reduce the risk of preterm birth. The concept of the 'incompetent' cervix has now been refined and replaced with a model of a preterm parturition 'syndrome'; with interaction between cervical function, vaginal flora, and the maternal immune system and inflammatory response [14]. Hence, the previous commonly used intervention of cervical cerclage has been challenged. Cervical cerclage is an intervention that has been widely used with a limited evidence base. The only previous randomised trial of cerclage carried out over 30 years ago indicated that its use conferred a reduction in risk of preterm birth before 33 weeks from 18 to 13% [15].

Further studies since then support a reduction in preterm birth risk for cerclage insertion in high risk women [16]. Cerclage insertion is now commonly used either as an elective procedure in women with multiple previous early preterm births, as an ultrasound-indicated procedure due to shortened cervix on scan, or as a 'rescue' procedure in women with a dilated cervix.

Vaginal Progesterone

It is, however, now clear that alternative interventions may have similar efficacy to cerclage in the prevention of preterm birth in the high risk population, most notably progesterone treatment and the use of the Arabin pessary. Progesterone has been used to reduce the risk of preterm birth in high risk women since 2003 [17, 18], particularly women with a short cervix on scan [19]. However, its use is controversial and clinical trials have given conflicting results regarding the benefit conferred. The largest, most recent UK trial suggested that it is of no benefit [20], although meta-analysis that includes this trial still favours progesterone use [21]. Internationally, guidelines differ, with advice from the American College of Obstetrics and Gynecology that states 'a woman with a singleton gestation and a prior spontaneous preterm singleton birth should be offered progesterone supplementation starting at 16–24 weeks of gestation, regardless of transvaginal ultrasound cervical length, to reduce the risk of recurrent spontaneous preterm birth' [22] and UK advice which recommends it only in selected women with a cervix length of less than 25 mm [23]. It is commonly used as an alternative to cervical cerclage in women with a short cervix. A number of studies are now trying to compare the efficacy of progesterone with cervical cerclage and the Arabin pessary in order to identify the best treatment option [24]. The Arabin pessary is more commonly used in Europe and has the advantage of being inserted and removed in the outpatient setting without the need for anaesthesia (see Fig. 1.2).

Abnormal vaginal flora, as indicated by a diagnosis of bacterial vaginosis especially in the first half of pregnancy, is recognised to have an association with preterm birth [25]. The role of routine screening and treatment with antibiotics remains controversial [26] and there is wide variation in the assessment and treatment of abnormal vaginal flora in the setting of the prematurity antenatal clinic [27].

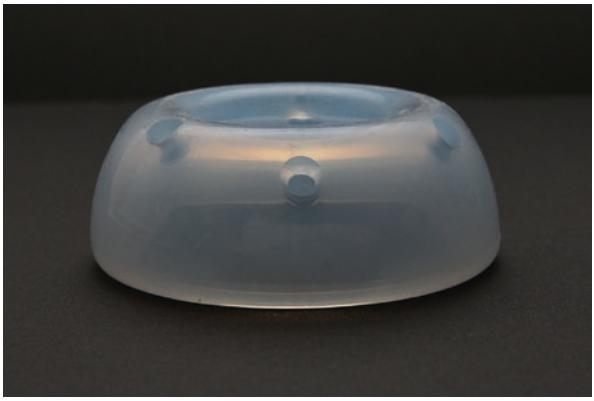


Fig. 1.2 The Arabin pessary is a flexible silicone ring that sits within the vagina and supports the cervix. (Figure supplied by Dr. Birgit Arabin, reproduced with permission)

Preterm Birth: Intrapartum Care

The intrapartum management of preterm labour is focused on optimising the condition of the preterm neonate. Whilst tocolysis is an attractive option, there is no evidence that it reduces the chance of preterm birth [28, 29]. Instead the aim is to delay the inevitable preterm birth by a few days to permit interventions that may benefit the baby. There is limited evidence that this strategy improves neonatal outcome; however that may be due to the age and limitations of the trials that have been carried out. All trials of tocolysis have limited power to demonstrate any benefit to the baby, as the majority of women presenting with threatened preterm labour will deliver at term irrespective of interventions undertaken. Tocolytics in current UK use include the oxytocin receptor antagonist atosiban, and nifedipine [23]. They should only be used where there is no evidence of fetal or maternal compromise, and where delay in delivery may be of benefit to the baby. Commonly this time delay would be used for administration of corticosteroids, magnesium sulfate, and for consideration of transfer to a tertiary unit if needed.

Corticosteroid administration prior to preterm deliveries is now routine practice to reduce risk of respiratory distress and its consequences. However maximal benefit is conferred if delivery is within a week of administration. If there is a significant time delay before preterm birth, then the risks of repeated course of steroids needs to be weighed up against the potential benefit. Current guidance is not to routinely give a second course of steroids but to consider it on an individual patient basis if there has been a significant time interval since the original course [23]. This is a horizon for future research.

Magnesium Sulfate

Intrapartum magnesium sulfate administration improves neurodevelopmental outcome in preterm infants [30] but the timing, as with steroids, can be difficult to optimise. Consensus is that administration should occur within 24 h of delivery and it should therefore be given to those women diagnosed as being in established preterm labour, or those in whom prelabour delivery is planned within 24 h. Although different regimes have been used in clinical trials, it appears that its administration confers approximately 30% reduction in risk of cerebral palsy in the surviving preterm baby [30, 31]. In the UK, administration is recommended prior to all births at less than 30 weeks of gestation, and consideration of administration up to 34 weeks [23].

Threshold of Viability

The greatest challenges for both the obstetric and neonatal teams are in dealing with babies born at the threshold of viability (22–25 weeks). Active resuscitation is attempted for 84% of those born between 23 + 0 and 23 + 6 weeks of gestation [32].

When in labour at the limits of viability fetal monitoring is challenging. Continuous cardiotocogram (CTG) may be technically impossible and cannot be interpreted using the same criteria used at term. A frank discussion, including the neonatal team, is required with women at high risk of delivering at the limits of viability. This discussion should include information on likely neonatal outcomes, and the limitation of monitoring and intervention. There is no evidence that delivery by Caesarean section at this gestation will improve the fetal/neonatal survival, but it may impact significantly on maternal morbidity in both the current and future pregnancies. It should then be questioned that if intervention is not to be carried out, there may be no value in monitoring of the fetal heartbeat continuously or even intermittently.

However the potential consequence of an intrapartum fetal death should be explained and discussed explicitly. This decision making should be individualised and cannot be standardised by a guideline [33].

Non-cephalic Presentation

In spontaneous preterm labour there is a higher incidence of breech presentation compared to at term, making decision making more difficult. A recent large systematic review has shown Caesarean section reduced severe intraventricular haemorrhage by 41% and death by 49% in the extreme preterm breech. The study was limited to those actively resuscitated and born at less than 28 weeks of gestation and the advantages were more apparent at earlier gestations [34]. The EPIPAGE-2 study looked at preterm breech births from 26 to 34 weeks of gestation and showed no improved outcomes, including survival without associated morbidity, by delivering by Caesarean section [35]. Unfortunately, at earlier gestations there is an increased risk of the need for upper segment Caesarean section which comes with higher maternal morbidity for this and subsequent pregnancies. This includes increased rates of post-partum haemorrhage, need for caesarean hysterectomy and greater risk of uterine scar dehiscence in future pregnancies [36].

Group B Streptococcus

Management of any preterm labour should also include consideration of antibiotic administration. Infection is a major underlying aetiology of preterm labour, especially at extreme preterm gestations. The ORACLE trial suggested that routine administration of broad spectrum antibiotics in preterm labour with intact membranes did not improve neonatal outcomes [37]. In the UK there is now a recommendation to give antibiotics for prophylaxis against Group B Streptococcus (GBS) to all women in established preterm labour, as the sequelae of GBS infection are more severe in the preterm neonate [38].

Stillbirth Prevention and Fetal Growth Surveillance

There are many new obstetric initiatives aiming to reduce rates of stillbirth. This has been highlighted as a major international priority. Reducing stillbirths will ultimately involve increasing iatrogenic preterm delivery and must be supported by the neonatal facilities to deal with this consequence.

International: 'Ending Preventable Stillbirth'

The Lancet 'Ending Preventable Stillbirth' series in 2016, highlighted the annual estimated stillbirth incidence of 2.6 million and noted that half of these occur during labour and birth [39]. Ninety percent of stillbirths occur in countries with lower incomes; they can often be associated with maternal infection, notably syphilis and malaria, and poor access to care. With appropriate resources and recognition many of these stillbirths can be prevented. The availability of worldwide stillbirth data has increased significantly. Sixty-eight countries had no available data in 2009 and this has dropped to 38 countries in 2015. It is noted that global leadership and responsibility is key to improving outcomes. The United Nations inter-agency group for Child Mortality Estimation has now taken overall responsibility for reporting rates and it is hoped this will improve data available for assessment. The Every Newborn Action Plan aims to reduce stillbirth in all countries, to less than 12 per 1000 births by 2030 [39]. Considering the international impact of stillbirth, it is proportionally underfunded.

The Lancet review recommends cohesive care, starting prenatally with health optimisation and access to contraception. Access to antenatal care, with adequate infection recognition and treatment and fetal surveillance, is required. Intrapartum care should include fetal monitoring and access to obstetric intervention if needed. It also recommends the de-stigmatisation of stillbirth with worldwide education and postnatal support for those affected. The burden is both psychological and financial, with many families struggling to return to work after such a traumatising event. Clearly the above ideology is sound, but implementing internationally in countries with poor resources and conflict or natural disaster will be complex.

It is important to recognise the shift may see stillbirth rates drop but an increase in neonatal deaths if neonatal support in a country is inadequate to deal with neonates with complications.

UK: Saving Babies' Lives

The above recommendations are already being implemented in most developed countries.

In the UK the 'Saving Babies Lives' care bundle, launched in 2016, and updated in 2019, aims to halve stillbirths by 2025. The care bundle includes improving smoking cessation, risk assessment and surveillance for fetal growth restriction, raising awareness of reduced fetal movements and effective fetal monitoring during labour [40]. In high income countries the stillbirth is often antenatal rather than intrapartum and may be associated with modifiable lifestyle factors such as obesity and smoking [41]. Smoking cessation can be improved with routine carbon monoxide (CO) testing at booking and cessation education given. Initial evaluation of the Saving Babies Lives care bundle has demonstrated good uptake of the themes outlined. CO testing was almost universally undertaken, and an increased proportion of small-for-gestational-age babies was identified antenatally (up from 33.8% to 53.7%). The stillbirth rates in the earlier adopter trusts fell by 20% [42].

Each Baby Counts

Running in parallel with 'Saving Babies Lives', 'Each Baby Counts' is a 5-year programme launched by the Royal College of Obstetricians and Gynaecologists in 2015 to reduce the rate of term intrapartum related stillbirths, neonatal deaths and brain injuries. It collects data and implements local reviews on all term intrapartum stillbirths, hypoxic ischaemic encephalopathy grade 3 and neonatal deaths, reviewing whether the event was avoidable and assesses the quality of the local review undertaken.

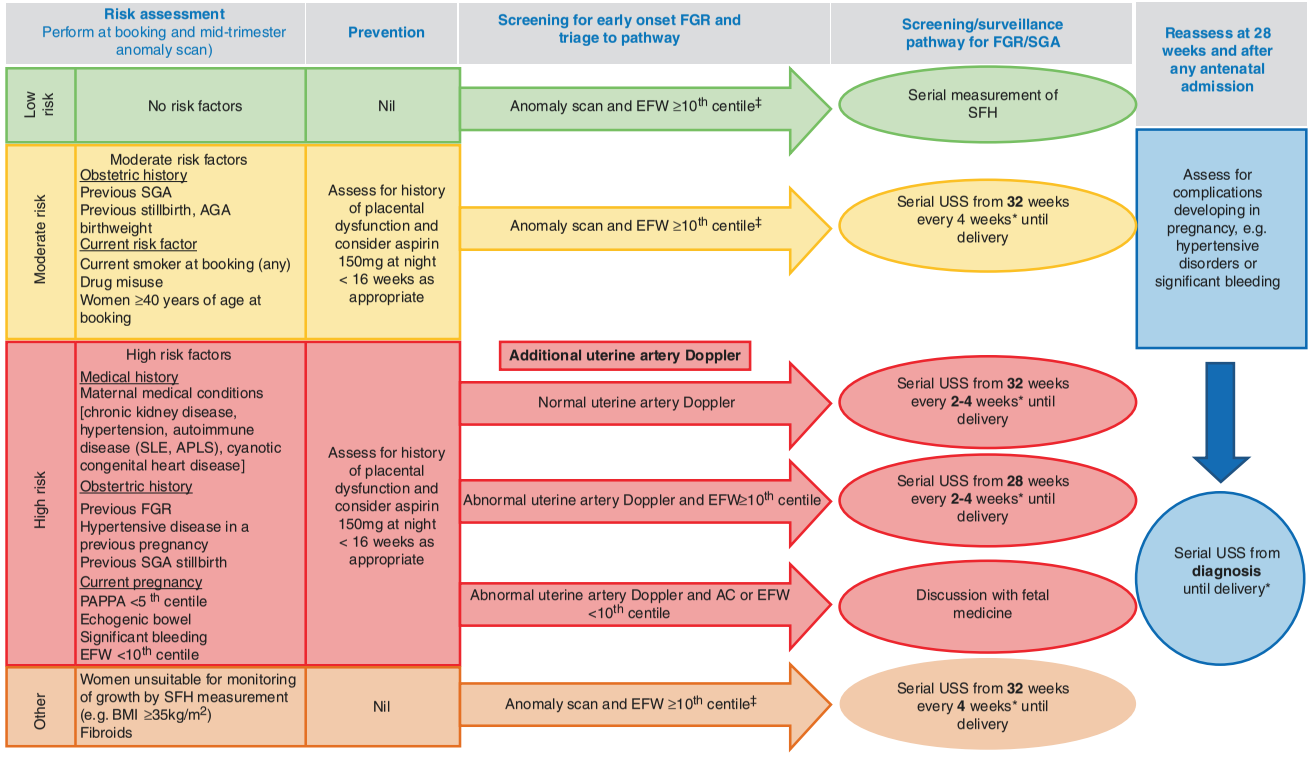
Obstetrics needs to strive to achieve safety levels that other industries such as aviation accomplish. Human factors training, popular in the aeronautical industry, is being implemented in many hospitals to improve situational awareness and reduce serious incidents [43, 44].

Fetal Growth Restriction

'Saving babies lives' highlights the need to monitor fetal growth as fetal growth restriction (FGR) is a major risk factor for stillbirth [44, 45]. Careful assessment of risk factors for FGR should be undertaken at booking for antenatal care (Fig. 1.3).

Women who are assessed to have no risk factors can then have growth surveillance with midwifery symphysis-fundal height assessments from 26 to 28 weeks of pregnancy, with growth scans only carried out if triggered by abnormal measurements or growth velocity. If major risk factors for FGR are identified at booking, then serial ultrasound growth assessments from either 28 weeks (if abnormal uterine artery Doppler) or 32 weeks are recommended [54].

If multiple minor risk factors are identified then the Royal College of Obestetricians and Gynaecologists currently recommend uterine artery Dopplers at the 20 week anomaly scan, with serial growth scans if these are abnormal. Clearly,



The risk factors listed here constitute those routinely assessed at booking, other risk factors exist and risk assessment must always be individualised taking into account previous medical and obstetric history and current pregnancy history. For women with maternal medica conditions and individuals with disease progression or institution of medical therapies may increase an individuals risk and necessitate monitoring with serial scanning. For women with aprevious stilbirth, management must be tailored to the previous history i.e. evidence of placental dysfunction or maternal medical conditions. Serial measurement should be performed as per NICE antenatal care guideline.
‡AC and/or EFW <10th centile at the anomaly scan is a high risk factory. *Refer to risk assessment and screening section for advice on scan interval.

Fig. 1.3 Saving Babies Lives Version 2 suggests this algoithm to stratify the type of fetal growth assessment used in singleton pregnancy. (From Saving Babies Lives Version 2, with permission [54])

this is dependent on risk factors being identified at booking and being reassessed at each contact with a healthcare professional.

Customised Growth Charts

There is a division of opinion, especially in the UK, regarding which growth charts should be used. Currently, the charts favoured by many UK hospitals are Gestational Related Optimum Weight (GROW) charts, which are also being used internationally [46]. They offer a customised chart showing the tenth and 90th centiles for a given woman, based on her height, weight, parity and ethnicity. An alternative system used is INTERGROWTH 21st (IG21) which uses a universal standard created from an apparent multi-ethnic population and is based on the premise that fetal growth should not differ by ethnicity in a well-nourished population [47]. Studies comparing both INTERGROWTH 21st and GROW have shown neither to be a perfect solution but IG21 highlighted 20% of babies were large for gestational age babies and only 4.4% SGA and this could be due to it being based on a much smaller cohort of countries.

GROW is based on a much larger multi-ethnic population and picks up more SGA babies and this cohort had a higher stillbirth rate. Those not picked up by IG21 as SGA still had a relative risk of stillbirth of 1.9 (95% CI 1.6–2.2). The highest relative risk for stillbirth (3.5; 95% CI, 3.1–4.1) was observed for babies identified as SGA by both IG21 and GROW although using both methods is clearly impractical [48].

Fetal Dopplers

Fetal growth scans are used to estimate fetal weight and undertake Doppler studies. The umbilical artery Dopplers are looked at in combination with fetal growth.

Early Onset, Small for Gestational Age

Early onset, severe small-for-gestational-age (SGA) fetuses need very careful assessment including fetal medicine review, with possible genetic investigation such as karyotyping and microarray analysis if available.

Infection screening for toxoplasmosis and cytomegalovirus is also required for this group, and for some high risk populations testing for maternal malaria and syphilis are performed.

Prior to 32 weeks, if the umbilical artery Dopplers demonstrate an increased pulsatility index (PI) or resistive index (RI), then increased surveillance is appropriate. If end diastolic umbilical artery blood flow is absent or reversed, then the ductus venosus wave form is analysed. Decisions about delivery in the early onset SGA baby should be made after careful joint counselling with the neonatal team, and the prognosis offered should take into account not only gestation, but the estimated fetal weight. It would be unusual to offer delivery with an estimated fetal weight of less than 500 g, due to the very poor prognosis.

Antenatal corticosteroids should be considered when preterm delivery appears likely, and magnesium sulfate should be administered once the decision for delivery is made.

Late Onset SGA

Later onset SGA is more likely to be due to placental dysfunction. In the UK, NICE recommends use of aspirin to be commenced prior to 16 weeks of gestation for those at risk of pre-eclampsia to reduce risk of pre-eclampsia and improve SGA incidence in this cohort [49]. In addition to umbilical artery Doppler studies, in the third trimester, the middle cerebral artery (MCA) Doppler study can be undertaken to look for redistribution and cerebral sparing secondary to hypoxia. A reduced MCA PI of below 5% would suggest an increased cerebral blood flow and in combination with increased umbilical PI would be a sign of growth restriction. The cerebro-placental ratio less than 1 has been shown to be a predictor of stillbirth and of need for emergent intrapartum delivery following CTG concerns [50, 51].

Dawes Redman CTG

Abnormal growth and Dopplers at earlier preterm gestations can necessitate inpatient stays and frequent Doppler assessments until delivery. The midwife can use the Dawes Redman CTG to provide additional information in-between ultrasound Doppler assessments. Dawes Redman CTGs electronically assess non-labouring fetuses [52]. This computerised model has learned from a bank of 100,000 CTGs and can more quickly conclude the CTG as being normal (‘meeting the Dawes Redman criteria’). It is important to also incorporate clinical history and ongoing concerns when deciding to take off and stop the electronic CTG. The output it creates is complex and can be poorly understood by all labour ward staff, if criteria is not met at 60 min. However, if used correctly it can function to pick up potentially hypoxic babies that could be missed with conventional CTG and visual human interpretation.

Impact on Neonates

Increasing fetal surveillance techniques and timed use of corticosteroids has allowed the obstetrician to opt to deliver to try to avoid stillbirth and has also improved neonatal morbidity and mortality within the iatrogenic preterm birth group. Subsequently, iatrogenic preterm birth has increased over recent years.

A large population review in the USA showed an increase in iatrogenic preterm birth from 2.2 in 1995 to 3.7 per 100 live births in 2005 (odds ratio = 1.77, 95%CI:1.76–1.79), whereas spontaneous preterm rates are fairly stable [53].

Ultimately, regardless of the choice of pathway followed, the ultrasonography resource requirement to improve detection of the SGA baby and reduce stillbirth risk will be significantly increased. They will also need to postnatally review any false negatives and false positives created by their programme and adapt to improve accuracy. Those that have been shown as falsely SGA by these methods may have been subjected to unnecessary intervention whether that be induction or Caesarean. Those that are not correctly identified as SGA will not have been induced or delivered in a timely manner and will therefore inadvertently been subjected to an increased risk of stillbirth.

Conclusion

The care of the preterm infant has improved dramatically, due to advances in both obstetric and neonatal management. The identification of those at high risk of preterm birth needs more research, to enable treatments such as pessaries, cerclage or progesterone to be targeted. When preterm birth is threatened or occurring, obstetric antenatal care can include interventions to improve lung maturation, neurodevelopment and to reduce risk of neonatal sepsis. This aims to reduce neonatal admissions and long term follow up.

The increased international drive to reduce stillbirth will identify more small-for-gestational-age babies, which are likely to require iatrogenic preterm delivery. This may cause additional strain on neonatal services but with the reduction in stillbirth and its devastating sequelae for the families, this may be a small price to pay.

References

1. Saigal S, Doyle L. Preterm birth 3. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet. 2008;371:261–9.
2. Goldenberg R, Culhane J, Iams J, Romero R. Preterm birth 1. Epidemiology and causes of preterm birth. Lancet. 2008;371:75–84.
3. Haines N. Office of national statistics. Birth summary tables England and Wales 2016. Updated 2016. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthsummarytablesenglandandwales/2017. Accessed 19 Oct 2019.

4. Iams J, Romero R, Culhane J, Goldenberg R. Preterm birth 2. Primary, secondary and tertiary interventions to reduce the morbidity and mortality of preterm birth. Lancet. 2008;371:164–75.
5. Sharp N, Alfivirec Z. Provision and practice of specialist preterm labour clinics: a UK survey of practice. BJOG. 2014;121:417–21.
6. Berghella V, Gimovsky A, Levine L, Vink J. Cesarean in the second stage: a possible risk factor for subsequent spontaneous preterm birth. Am J Obstet Gynecol. 2017;217:1–3.
7. Watson H, Carter J, David A, Seed P, Shennan A. Full dilatation caesarean section: a risk factor for recurrent second-trimester loss and preterm birth. Acta Obstet Gynecol Scand. 2017;96:1100–5.
8. Wood S, Tang S, Crawford S. Cesarean delivery in the second stage of labor and the risk of subsequent premature birth. Am J Obstet Gynecol. 2017;217(63):e1–10.
9. Cong A, De Vries B, Ludlow J. Does previous caesarean section at full dilatation increase the likelihood of subsequent spontaneous preterm birth? Aust N Z J Obstet Gynaecol. 2018;58:267–73.
10. Nott J, Pervolaraki E, Benson A, et al. Diffusion tension imaging determines three-dimensional architecture of human cervix: a cross-sectional study. BJOG. 2018;125:812–8.
11. Corry E, Ramphul M, Rowan A, Segurado R, Mahony R, Keane D. Exploring full cervical dilatation caesarean sections—a retrospective cohort study. Eur J Obstet Gynecol Reprod Biol. 2018;224:188–91.
12. Seal S, Dey A, Barman S, Kamilya G, Mukherji J, Onwude J. Randomized controlled trial of elevation of the fetal head with a fetal pillow during caesarean delivery at full cervical dilatation. Int J Gynaecol Obstet. 2016;133:178–82.
13. Crane J. Use of transvaginal ultrasonography to predict preterm birth in women with a history of preterm birth. Ultrasound Obstet Gynecol. 2008;32(5):640–5.
14. Gotsch F, Romero R, Erez O. The preterm parturition syndrome and its implications for understanding the biology, risk assessment, diagnosis, treatment and prevention of preterm birth. J Matern Fetal Neonatal Med. 2009;22:5–23.
15. MRC/RCOG Working Party on Cervical Cerclage. Interim report of the medical research council/royal college of obstetricians and gynaecologists multicentre randomized trial of cervical cerclage. Br J Obstet Gynaecol. 1988;95:437–45.
16. Alfirevic Z, Stampalia T, Medley N. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. Cochrane Database Syst Rev. 2017;6:CD008991. https://doi.org/10.1002/14651858.CD008991.pub3.
17. Meis P, Klebanoff M, Thom E. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003;348:2379–85.
18. Da Fonseca E, Bittar R, Carvalho M, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol. 2003;188:419–24.
19. Fonseca E, Celik E, Parra M, Singh M, Nicolaides K. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med. 2007;357:462–9.
20. Norman J, Marlow N, Messow C, Shennan A, Bennett P, Thornton S. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. Lancet. 2016;387(10033):2106–16.
21. Romero R, Nicolaides K, Conde-Agudelo A. Vaginal progesterone decreases preterm birth ≤34 weeks of gestation in women with a singleton pregnancy and a short cervix: an updated meta-analysis including data from the OPPTIMUM study. Ultrasound Obstet Gynecol. 2016;48:308–17.
22. ACOG. Prediction and prevention of preterm birth. Practice bulletin 130. Obstet Gynecol. 2012;120:964–73.
23. National Institute for Health and Care Excellence. Preterm labour and birth. NICE guideline NG25. Updated 2015. https://www.nice.org.uk/guidance/ng25.
24. Hezelgrave N, Watson H, Ridout A. Rationale and design of SuPPoRT: a multi-centre randomised controlled trial to compare three treatments: cervical cerclage, cervical pessary and

vaginal progesterone, for the prevention of preterm birth in women who develop a short cervix. BMC Pregnancy Childbirth. 2016;16:358.
25. Hay P, Lamont R, Taylor-Robinson D, Morgan D, Ison C, Pearson J. Abnormal colonisation of the genital tract and subsequent preterm delivery and late miscarriage. BMJ. 1994;308:295–8.
26. Haahr T, Ersboll A, Karlsen M. Treatment of bacterial vaginosis in pregnancy in order to reduce the risk of spontaneous preterm delivery—a clinical recommendation. Acta Obstet Gynecol Scand. 2016;95:850–60.
27. Brocklehurst P, Jordon A, Heatley E, Milan S. Antibiotics for treating bacterial vaginosis in pregnancy. Cochrane Database Syst Rev. 2013;(1):CD000262.
28. Gyetvai K, Hannah M, Hodnett E, Ohisson A. Tocolytics for preterm labour: a systematic review. Obstet Gynacol. 1999;94(869):877.
29. Flenady V, Reinebrant H, Liley H, Tambimuttu E, Papatosonis-Dimitri N. Oxytocin receptor antagonists for inhibiting preterm birth. Cochrane Database Syst Rev. 2014;(7):CD006169.
30. Peebles D, Kenyon A. Magneisum sulphate to prevent cerebral palsy following preterm birth. Scientific impact paper 29. Magnesium sulphate to prevent cerebral palsy following preterm birth scientific impact paper no. 29. RCOG. 2011.
31. Rouse D, Hirtz D, Thom E, Varner M, Spong C, Mercer B. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. N Engl J Med. 2008;359:895–905.
32. Costeloe K, Hennessy E, Haide S, Stacey F, Marlow N, Draper E. Short term outcomes after extreme preterm birth in england: comparison of two birth cohorts in 1995 and 2006 (the EPICURE studies). BMJ. 2012;345:7976.
33. David A, Soe A. Extreme prematurity and perinatal management. Obstetr Gynaecol. 2018;20(109):117.
34. Grabovac M, Karim J, Isayama T, Liyanage S, McDonald S. What is the safest mode of birth for extremely preterm breech singleton infants who are actively resuscitated? A systematic review. BJOG. 2018;125(6):652–63.
35. Lorth E, Sentilhes M, Quere M, et al. Planned delivery route of preterm breech singletons and neonatal and 2-year outcomes: a population-based cohort study. BJOG. 2019;126:73–82. https://doi.org/10.1111/1471-0528.15466.
36. Greene R, Fitzpatrick C, Turner M. What are the maternal implications of a classical caesarean section? J Obstet Gynaecol. 1998;18:345–7.
37. Kenyon S, Taylor D, Tarnow-Mordi W. Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised trial. ORACLE collaborative group. Lancet. 2001;357(9261):989–94.
38. Royal College of Obstetricians and Gynaecologists. Prevention of early-onset neonatal group B streptococcal disease. BJOG. 2017;124(12):e280–305.
39. De Bernis L, Kinney M, Stones W. The lancet ending preventable stillbirths series study group with the lancet ending preventable stillbirths series advisory group. stillbirths: Ending preventable deaths by 2030. Lancet. 2016;387:703–16.
40. O'Connor D. Saving babies lives. A care bundle for reducing stillbirths. NHS England 26th. Updated 2016. https://www.england.nhs.uk/wp-content/uploads/2016/03/saving-babies-lives-car-bundl.pdf. Accessed 19 Oct 2018.
41. Flenady V, Wojcieszek A, Middleton P. The lancet ending preventable stillbirths study group and the lancet stillbirths in high income countries investigator group. Stillbirths: recall to action in high-income countries. Lancet. 2016;387:691–702.
42. Widdows K, Roberts S, Camacho E, Heazell A. Saving babies' lives project impact and results evaluation (SPiRE): a mixed methodology study. BMC Pregnancy Childbirth. 2018;30(1):43.
43. Jackson K, Hayes K, Hinshaw K. The relevance of non-technical skills in obstetrics and gynaecology. Obstetr Gynaecol. 2013;15(4):269–74.
44. National Quality Board. Never? Appendix 2, Department of Health Human Factors Reference Group interim report. Updated 2012. http://www.england.nhs.uk/wp-content/uploads/2013/11/DH-2.pdf. Accessed 30 Jul 2018.

45. Gardosi J, Madurasinghe V, Williams M, Malik A, Francis F. Maternal and fetal risk factors for stillbirth: population based study. http://www.bmj.com/content/346/bmj.f108.
46. Gardosi J, Francis A, Turner S, Williams M. Customized growth charts: rationale, validation and clinical benefits. Am J Obstet Gynecol. 2018;218:S609–18.
47. Papageorghiou A, Ohuma E, Altman D. International standards for fetal growth based on serial ultrasound measurements: the fetal growth longitudinal study of the INTERGROWTH-21st project. Lancet. 2014;384:869–79.
48. Francis A. Customized vs INTERGROWTH-21st standards for the assessment of birthweight and stillbirth risk at term. Am J Obstet Gynecol. 2018;218(2):S692–9.
49. NICE. Hypertension in pregnancy guideline. https://www.nice.org.uk/guidance/cg107/resources/hypertension-in-pregnancy-diagnosis-and-management-pdf-35109334011877. Accessed 19 Oct 2018.
50. DeVore G. The importance of the cerebroplacental ratio in the evaluation of fetal well-being in SGA and AGA fetuses. Am J Obstet Gynecol. 2015;213(1):5–15.
51. Khalil A, Morales-Roselló J, Townsend R, et al. Value of third-trimester cerebroplacental ratio and uterine artery doppler indices as predictors of stillbirth and perinatal loss. Ultrasound Obstet Gynecol. 2016;47(1):74–80.
52. Dawes G, Lobb M, Moulden M, Redman C, Wheeler T. Antenatal cardiotocogram quality and interpretation using computers. BJOG. 1992;99:791–7.
53. Lisonkova S, Hutcheon J, Joseph K, et al. BMC Pregnancy Childbirth. 2011;11:39. https://doi.org/10.1186/1471-2393-11-39.
54. NHS England. Saving Babies Lives Version 2. A care bundle for reducing perinatal mortality. Updated 2019. https://www.england.nhs.uk/wp-content/uploads/2019/05/saving-babies-lives-care-bundle-version-two.pdf. Accessed 26 Jun 2019.

Chapter 2
Maternal Chronic Conditions and the Fetus

Kate Jones, Abigail Anness, and Farah Siddiqui

Pre-conception Care

Pre-conception care (PCC) is the provision of interventions to women prior to conception. It aims to improve their health status and change behaviours that contribute towards poor maternal and child outcomes [1]. PCC provides the opportunity to review a woman's disease status, change medication regimes to avoid teratogens and perform baseline investigations (for example, retinopathy and renal function screening for those with diabetes). Women with suboptimal disease control may be advised to defer pregnancy until their disease has been stabilised in order to lower the risk of adverse maternal or fetal outcomes. Women at a higher risk of neural tube defects will be advised to take 5 mg (rather than the standard 400 μg supplement) of folic acid daily. The pre-conception counselling should also include a frank discussion regarding a healthy diet, target body mass index and smoking cessation.

Pre-conception care is associated with decreased rates of congenital malformations [2] in women with epilepsy and pre-existing diabetes. It is also associated with improved glycaemic control in the first trimester and decreased perinatal mortality in women with pre-existing diabetes [2]. Ideally PCC should be provided to all women with chronic medical conditions.

Epilepsy

Annually there are approximately 2500 pregnancies in the UK in women with epilepsy [3]. Most pregnancies have a good outcome; however epilepsy had the highest maternal mortality rate for any medical condition in the 2015 Mothers and Babies;

K. Jones · A. Anness · F. Siddiqui (✉)
Department of Fetal and Maternal Medicine, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester, UK
e-mail: farah.siddiqui@uhl-tr.nhs.uk

E. M. Boyle, J. Cusack (eds.), *Emerging Topics and Controversies in Neonatology*, https://doi.org/10.1007/978-3-030-28829-7_2

Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK) report [3, 4] so it is important that these patients are carefully managed in the multidisciplinary clinic.

Preconception Advice

Pre-conception counselling aims to achieve seizure control with the lowest dose of antiepileptic drug (AED), avoiding polytherapy where possible. Women with epilepsy should take 5 mg of folic acid pre-conceptually and throughout the pregnancy to reduce the risk of neural tube defects and long-term cognitive deficits [5].

Maternal and Fetal Implications

Antenatal care seeks to achieve seizure control whilst minimising the potential teratogenic effects of AEDs. Seizures in pregnancy are associated with a risk of cerebral palsy and fetal death, and sudden unexpected death in epilepsy (SUDEP) is more common in poorly controlled disease [5]. The physiological increase in plasma volume associated with pregnancy can alter serum AED levels so dose adjustments may be required during pregnancy. AEDs are associated with an increased risk of congenital malformations (mainly cardiac defects, facial clefts and neural tube defects) and cognitive deficits [4, 5]. This risk is dose dependent and increases with polytherapy [4]. Carbamzepine, lamotrigine, levetiracetam and phenytoin carry the lowest risks (1–5%). Sodium valproate carries the highest risk (6–10%) and its use in women of childbearing age is restricted by Medicines and Healthcare products Regulation Authority (MHRA) regulations whose guidance about Valproate use in pregnancy has recently been updated [6].

Delivery and Postnatal

Epilepsy is not usually an indication for induction of labour or Caesarean section. The risk of maternal seizures is greatest around the time of delivery and immediately post-partum. Seizures in labour should be treated promptly with intravenous or rectal medication, usually a benzodiazepine, as they may lead to fetal hypoxia or injury if a fall is sustained [5].

Babies born to women with epilepsy taking enzyme inducing AEDs should be offered 1 mg of intramuscular vitamin K to prevent haemorrhagic disease of the newborn [5]. Whilst this is offered to all infants in the UK, its importance for this group of patients should be emphasised. Most AEDs are secreted into breast milk but only low levels are absorbed by the neonate, so women should be encouraged to

breast feed. There is a theoretical risk of withdrawal in the neonate if the mother is taking AEDs antenatally—breast feeding may reduce this risk due to the small doses in the milk [7]. Women with epilepsy and their families should be advised of safety measures such as sitting on the floor to feed, avoiding co-sleeping and not bathing the baby alone.

Cardiovascular Disease

Advances in surgical techniques for the management of congenital heart disease, mean that children with these conditions are increasingly surviving into adulthood, allowing them to have children of their own. The details and outcomes of congenital heart disease surgery in children are discussed elsewhere in this book; here we discuss the management of pregnancy in women with corrected congenital heart disease.

Preconception Advice

Cardiac disease is the leading cause of indirect maternal deaths, with a rate of 2.34 per 100,000 maternities [3]. Women with known complex cardiac disease of reproductive age should be offered contraception; those considering embarking on a pregnancy should be assessed in a pre-conception clinic. Pregnancy is relatively contraindicated in the presence of pulmonary hypertension (25–40% mortality rate [7]), severe aortic or mitral stenosis, cyanotic heart disease or in the presence of poor left ventricular function [8]. Women with cyanotic heart disease have an increased risk of congenital malformation, miscarriage, fetal death and fetal growth restriction [9].

Maternal and Fetal Implications

Antenatal care is usually based around symptom control, such as management of arrhythmias, or reduction in cardiac pre-load. Medications most commonly used in pregnancy for cardiac disorders include beta-blockers, flecainide and digoxin. Women taking warfarin pre-pregnancy will usually be changed to a low molecular weight heparin, with haematological advice. Beta-blockers can cross the placental barrier and may be associated with growth restriction, respiratory depression, neonatal bradycardia and hypoglycaemia [8, 10]. These effects are more pronounced if the drugs are commenced in the first trimester. Women with complex disease and those on medication should be offered serial ultrasound assessments of fetal growth and wellbeing. If a maternal arrhythmia is refractory to medical treatment

or there is cardiogenic shock, electrical cardioversion may be required. Case reports suggest that electrical cardioversion should be considered safe in pregnancy; it should ideally be carried out with facilities available for continuous fetal monitoring and emergency caesarean although maternal health is the main consideration [11, 12]. Patients in cardiac failure may require extracorporeal membrane oxygenation (ECMO) which is discussed later in this chapter. Congenital cardiac conditions in either parent increase the risk of a fetal cardiac defect by 2–5% (background risk 1%), so a fetal echocardiogram may be offered.

Delivery and Postnatal

The timing, location and mode of delivery in a patient with cardiac disease will vary depending on the severity of the maternal condition and the resources in the booking hospital. Complex disorders, such as aortic root dilatation or a history of life-threatening arrhythmia, may require transfer to a specialist centre for delivery. Severe or deteriorating disease is likely to result in a preterm delivery, often by caesarean section. Where a vaginal birth is planned, shortening the second stage should be considered (for example by performing an instrumental delivery) and care with uterotonic medication such as ergometrine and syntocinon. Unless contra-indicated, epidural anaesthesia is often advised as it helps to maintain stability in blood pressure, but this is assessed on an individual basis by the multidisciplinary team.

Infants of women taking antenatal beta-blockers may require neonatal assessment for respiratory depression, bradycardia and hypoglycaemia [8, 10].

Hypertension

Hypertension in pregnancy may be pre-existing, pregnancy induced hypertension (PIH) or a component of pre-eclampsia (PET) [7]. Hypertension is the most common medical problem in pregnancy, affecting 10–15% of all pregnancies [7] and 8–10% of all preterm births result from hypertensive disorders [13]; PET is the most common cause of iatrogenic prematurity.

Preconception Advice

Pre-conception counselling should include an assessment of end organ damage, evaluation for secondary causes, weight loss if obese and optimisation of drug treatment.

Maternal and Fetal Implications

Women with hypertension require 75 mg aspirin from 12 weeks of gestation as prophylaxis for PET. In the UK, all pregnant women have their blood pressure measured and urine checked for protein at every antenatal visit in order to screen for PET. If detected they will undergo investigations to assess severity, including quantification of proteinuria, renal and liver function tests and platelet counts. They may require anti-hypertensive treatment, usually methyldopa, labetalol or nifedipine. Women with pre-existing hypertension or PET are at risk of fetal growth restriction and should have serial ultrasound scans for fetal growth. Severe pre-eclampsia carries maternal risks of eclampsia, intracranial haemorrhage, pulmonary oedema and placental abruption. It should be managed in a high-dependency setting—intravenous magnesium sulphate is used for maternal seizure prophylaxis.

Delivery and Postnatal

Delivery is the only cure for PET and in severe disease preterm delivery is often needed. Regional anaesthesia is encouraged unless there is thrombocytopenia with platelet counts less than 60–80 × 10^9/l[13].

Respiratory Disease

Asthma

Asthma affects up to 7% of women of reproductive age and is regularly encountered in pregnancy [7, 14].

Maternal and Fetal Implications

Women with mild asthma are unlikely to encounter problems but those with severe disease are at risk of deterioration of their asthma as well as an increased risk of fetal growth restriction and pre-eclampsia [14, 15]. These women should be offered fetal surveillance accordingly. Reducing or stopping medication is a common cause of symptom deterioration in pregnancy. Women should be encouraged to continue treatment and seek help promptly if unwell. In addition to common environmental triggers, maternal smoking, maternal obesity and antenatal exposure to respiratory viral infections are particularly significant risk factors for severe exacerbation of asthma [15]. Acute severe exacerbations should be treated aggressively using the

stepwise approach of the British Thoracic Society/Scottish Intercollegiate Guidelines Network guidelines or equivalent that are also used in non-pregnant patients [16]. Close liaison with respiratory physicians can aid management strategies for women with complex or brittle asthma, particularly during the third trimester. Most medications used to treat asthma appear to be safe in pregnancy and during lactation [7, 14].

Tuberculosis

The UK national incidence of tuberculosis was 4.2 per 100,000 pregnancies in 2008 [17]. It is most prevalent in women of ethnic minorities.

Maternal and Fetal Implications

Pregnancy is not an independent risk factor for tuberculosis (TB) and does not affect the clinical course of the disease [18]. Effective treatment usually results in normal pregnancy outcomes but delayed diagnosis, ineffective treatment or disseminated disease increases the risk of pre-eclampsia, maternal respiratory failure, fetal growth restriction and preterm delivery [18]. Treatment regimens are similar to those used outside pregnancy, although streptomycin should be avoided as it can cause fetal ototoxicity [19]. A typical treatment regimen may last 6–12 months and include isoniazid, rifampicin and ethambutol together with pyridoxine to reduce the risk of isoniazid-induced neuropathy.

Postnatal

All drugs are considered to be safe for breast feeding. Neonates should be treated with prophylactic isoniazid for 3 months if the mother is sputum positive [7]. The Bacillus-Calmette-Guerin (BCG) vaccine is offered to neonates at risk of TB exposure (based on family history or geographical location) [20].

Congenital TB, caused by vertical transmission, is rare [18]. It may occur where there has been delayed diagnosis or ineffective treatment of maternal TB. Infants present with symptoms at 2 or 3 weeks of age.

Cystic Fibrosis

The improving survival rates of women with cystic fibrosis (CF) mean there are increasing numbers of pregnancies in this high-risk population.

Preconception Advice

CF is the most common autosomal recessive disorder in the United Kingdom. Preconception genetic counselling and partner screening should be offered to all women who are known to be carriers of a CF gene or who have a relative with CF. In cases where the partner is also carrier or unavailable for testing, the choice of a chorionic villus sampling or amniocentesis should be offered, as some women may choose to discontinue their pregnancy if the fetus is affected.

Maternal and Fetal Implications

Pregnancy outcomes are related to pre-pregnancy lung function and disease status, and many women will tolerate pregnancy well. Outcomes are worse in women with FEV1 less than 60% predicted and pregnancy is contraindicated in the presence of cor pulmonale or pulmonary hypertension [7, 21]. The mainstay of antenatal care is physiotherapy, nutritional support and aggressive treatment of pulmonary infections, as well as regular assessment of fetal growth [22]. Maternal complications may include weight loss, infective exacerbations, unpredictable loss of lung function and congestive cardiac failure. The most common pregnancy complications are prematurity (25% [21, 22]) and fetal growth restriction. Poor maternal weight gain is predictive of preterm delivery and stillbirth. There is also a risk of maternal gestational diabetes and its associated complications.

Gastro-Intestinal Disorders

Inflammatory Bowel Disease

Quiescent inflammatory bowel disease (IBD) is not associated with adverse pregnancy outcomes; however, active Crohn's disease or ulcerative colitis at the time of conception is associated with a higher risk of complications. These include miscarriage, stillbirth, preterm delivery and growth restriction [23, 24]. Children of parents with inflammatory bowel disease have an increased risk of developing IBD.

Maternal and Fetal Implications

Antenatal care focuses on maternal disease control. Azathioprine, sulphasalazine and mesalazine are safe in pregnancy and breast feeding. Sulphasalazine interferes with folate absorption, therefore women should take 5 mg of folic acid. Corticosteroids can be used to manage flares—transplacental passage of steroids does occur, but rapid metabolism by the fetus leads to low fetal blood concentration.