COMPASS Therapeutic Notes on the Management of Chronic Conditions in Pregnancy and Breastfeeding

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Glossary of terms	
The Apgar test	A quick assessment of a newborn baby's health and vital functions, performed at 1 and 5 minutes after birth
Macrosomia	Newborn with an excessive birth weight
Shoulder dystocia	The baby's head has been born but one of the shoulders becomes stuck behind the mother's pelvic bone, preventing the birth of the baby's body[176]
Polyhydramnios	An excessive amount of amniotic fluid surrounding the fetus.
Oligohydramnios	A deficiency of amniotic fluid
Erb's palsy	Arm weakness/loss of motion
Epicanthal folds	Skin of the upper eyelid that covers the inner corner of the eye
Hypertelorism	Abnormally increased distance between two organs
Philtrum	Midline groove in the upper lip that runs from the top of the lip to the nose
Microstomia	Reduction in the size of the oral aperture
Distal phalangeal hypoplasia (onychonychia)	Underdeveloped or missing end bones in fingers and toes as well as nail abnormalities ranging from underdeveloped to completely absent.
Gestational age	The length of pregnancy after the first day of the last menstrual period
Conceptional age	The length of pregnancy from the time of conception

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Introduction

Prescribing in women of child-bearing age

It is estimated that in one-third of births in the UK pregnancy is unplanned.[7] Therefore when treating a woman of child bearing age, especially for a chronic condition, healthcare professionals should consider the potential for pregnancy, whether planned or unplanned. If medication is prescribed this should be for a drug that is considered low risk in pregnancy. Likelihood of pregnancy and/or contraception should be considered each time a drug is prescribed to someone of child bearing age.

Pre-pregnancy counselling for women with chronic conditions

Women with chronic illness should always be advised to plan their pregnancies. Women desiring pregnancy should have pre-pregnancy counselling. This is the ideal opportunity to review all medication and optimise therapy for mother and fetus.

Women who take medication for chronic illness should be advised not to stop any of their medication abruptly if they discover they are pregnant. They should continue to take their medication as prescribed but discuss continued use with the most appropriate clinician (either consultant obstetrician or GP) as soon as possible.

Medication use in pregnancy

Approximately 50% of pregnant women take a prescription drug at some point during pregnancy and 10% of pregnant women have a chronic medical disorder that requires regular use of medicines.[1,2] Increasing age of conception and increasing body mass index (BMI) of the population has contributed to a greater number of women who require medication during pregnancy,[4] particularly for conditions such as type 2 diabetes and hypertension.

A need to be pragmatic

A cautious approach is warranted, but it is not always possible to stop all medication during pregnancy. Potential risks should be clarified to aid good clinical decision-making. It is important that risks and benefits of both treatment and stopping treatment are accurately portrayed to the woman in a balanced manner.[3]

Problems with adherence to medication during pregnancy

Adherence to medication in pregnancy can be poor.[6] Women may already have stopped taking their medication when they first present to the GP with the pregnancy.[3] Pregnant women tend to perceive their teratogenic risk of medications as significantly higher than the true risk.[158] Indeed some pregnant women avoid taking therapy, even for life-threatening medical conditions.[78]

Risk per trimester

Teratogenicity is the potential for a drug to cause fetal malformations. The greatest teratogenic risk is 3 to 8 weeks after conception (5 to 10 weeks gestation).[3] Stopping a drug after week 10, because of concerns about teratogenesis, therefore does not usually reduce the risk substantially.[3]

Fetotoxicity refers to the functional changes that can occur to the fetus as a result of medication. These effects are more subtle and more difficult to assess and therefore there are fewer data to support or refute these types of associations.[3] Fetotoxicity can occur anytime between the late first trimester and birth.[3] An example of fetotoxicity is the association between NSAIDs and premature closure of the ductus arteriosus in the third trimester.[3]

Neurodevelopmental disorders refer to potential effects of drugs on cognitive function by interference with brain development. It is not known when specific functional neurodevelopmental effects occur.[3] They are less obvious and harder to detect than structural anomalies. A longer follow-up period, into childhood, is required and several studies are on-going.

What is the baseline risk of birth defects and miscarriage?

It is important to note that birth defects and miscarriages can happen in *any pregnancy*, even to those who have not taken any medication or been exposed to chemicals.[6]
The risk of major malformation in the general population is 2%, and 10 to 20% of pregnancies end in a miscarriage.[3,6]

Effect of pregnancy on drug pharmacokinetics

There is reduced absorption and increased elimination of most drugs, resulting in reduced total plasma drug concentration. Also, the proportion of free drug to protein-bound drug may alter. This has implications for therapeutic drug monitoring, particularly for drugs with a narrow therapeutic window, e.g. lithium and phenytoin. Changes in dose should be guided by free levels or clinical need.
Changes in metabolism and renal clearance mean that for some drugs, an increased dose is required, e.g. insulin.

Unlicensed use of medicines in pregnancy

When prescribing medicines to pregnant women that are not licensed for use in pregnancy, informed consent should be obtained and documented.[46]

What about paternal exposure?

It is unusual for an increased risk of congenital malformations to be associated with exposure to drugs and/or chemicals in the father alone, except those that cause chromosomal abnormalities/point mutations, e.g. cytotoxic drugs. In practice, it is advisable to wait about six months (two sperm cycles) after paternal exposures to such drugs.[6]

Principles of prescribing in pregnancy

► Consultation of the most up-to-date resources should be used for specific drugs.
► Ask is the drug necessary?
► Use the minimum dose required to obtain the desired effect.[3]
► Absence of data does not imply safety.[3]
► Use drugs that have been used extensively in pregnancy, not new ones.[3]
► Be aware that the risk v benefit ratio may change depending on disease activity and stage of pregnancy, e.g. several biological therapies do not cross the placenta until well into the second trimester so may be considered in the first trimester for severe disease flare.
► Women with diabetes, coeliac disease, thalassaemia trait, those receiving anti–epileptic drugs, or women with a body mass index (BMI) of 30 kg/m^2 or more should take folic acid **5mg daily**.

What dose of folic acid should be recommended?

Women who are at normal risk for a neural tube defect should be advised to take folic acid **400 micrograms daily**, and to continue this until the 12th week of pregnancy.[253]

Risk of conceiving a child with a neural tube defect is increased if there is a personal or family history from either partner, or in women with **diabetes, coeliac disease, thalassaemia trait, those receiving anti–epileptic drugs, or in women with a body mass index (BMI) of 30 kg/m^2 or more**. Therefore these women should be advised to take a higher folic acid dose of **5mg daily**, and to continue this until the 12th week of pregnancy (until birth in women with thalassaemia trait).[253]

Use of drugs when breastfeeding

Almost every medicine has the potential to transfer into breast milk. However not all will cause harm to the infant. Breastfeeding offers many advantages to both mother and baby. Therefore it is important to determine the risk that each individual medicine poses and weigh this against the known benefits of breastfeeding.

What influences excretion of a drug into breast milk?

Chemical properties of a drug influence transfer into breast milk: lack of ionization, small molecular weight, low volume of distribution, low maternal serum protein binding, and high lipid solubility facilitate drug excretion into human milk.[28]

If it's OK in pregnancy is it OK in breast-feeding?

For most drugs, the infant is exposed to a much higher concentration during pregnancy than during lactation. Therefore, if the drug was considered acceptable during pregnancy, it is *usually* reasonable to continue it during breast feeding.[3] However, safety of specific drugs should always be checked.
Some drugs are not recommended in pregnancy but may be used in breastfeeding, e.g. warfarin, due to negligible amounts passing into breast milk.[123]

A decision to breastfeed when continuing treatment with an agent for which in utero exposure also has occurred differs from a decision to initiate a novel

therapy in the early postpartum period.[28] This will be discussed further under each chronic condition.

What about neonates and premature infants?

Neonates and particularly premature infants may be even more sensitive to maternal medication through breast milk. This is due to immature excretory functions and the consequent risk of drug accumulation.[3,28]
The risk of adverse reactions in a premature infant or an infant with underlying chronic medical conditions may be higher than that for a more mature or healthier infant.[28] Indeed, adverse events occur rarely in infants older than six months.[29]

Does timing of the feed matter?

It is often advocated that feeds should be timed to occur just before the mother takes a dose of medication, which could theoretically minimise the amount of drug the baby will ingest. In practice, this is rarely achievable, and counselling of the risks and benefits of a particular medication should not rely on this unrealistic option.[3]

Do some conditions contraindicate breastfeeding?

Some maternal health conditions may preclude breastfeeding, e.g. HIV. The need for multiple therapies by the mother that are particularly toxic, e.g. cancer treatment, will also make breastfeeding unsuitable.[28]
Some infant conditions, e.g. metabolic diseases may also preclude breastfeeding.[28]

Principles for prescribing in breastfeeding

► Safety (or lack of safety) in pregnancy does not necessarily extrapolate to breastfeeding.
► Drugs licensed for use in infants do not generally pose a hazard.[28]
► Small molecules get into breast milk more easily than large molecules. For example, heparin is not excreted in breast milk.[3]
► The risks of single-dose or short-term treatment may differ from those of chronic therapy, especially when adverse effects are additive, e.g. drowsiness.[28,123]
► Infants exposed to drugs via breast milk should be monitored for unusual signs or symptoms.[28]
► Avoid unnecessary drug use and limit use of over-the-counter (OTC) products.[123]
► Avoid long-acting preparations, especially with drugs likely to cause serious side effects (e.g. antipsychotic agents).[123]
► Avoid new drugs if a therapeutically equivalent alternative that has been used more widely is available.
► Choose a regimen and route of administration which presents the minimum amount of drug to the infant.[123]
► Avoid use of drugs with an unfavourable side effect profile, i.e. known to cause serious toxicity in adults or children, e.g. lithium, methotrexate.[28]

Information resources for medicines in pregnancy and breastfeeding

The most up to date reference sources should be used to evaluate specific drugs

- The UK Teratology Information Service website (www.uktis.org/index.html)
- UK Drugs in Lactation Advisory Service (UKDILAS) http://www.midlandsmedicines.nhs.uk
- UKMi Q&As www.evidence.nhs.uk (filter by Type of information 'Evidence Summaries' and Source 'UKMi').
- LactMed http://toxnet.nlm.nih.gov *
- BNF(www.bnf.org)
- NI Regional Medicines Information Service at Belfast Health and Social Care Trust (Weekdays 9am – 5pm, tel 028 9063 2032)

* LactMed is a US resource and therefore the conclusions and recommendations may not be the same as those produced by the UK Drugs in Lactation Advisory Service due to differences in practice and interpretation in the UK.[123]

Management of Asthma

Asthma is the most common medical condition encountered during pregnancy, occurring in 3 to 12% of all pregnancies.[124-128] The majority of women with asthma have normal pregnancies and the risk of complications is small in those with well controlled asthma.

What preconceptual care is recommended?

Pregnancy should be an indication to optimise therapy and maximise lung function in order to reduce the risk of acute exacerbation.[136]

Does pregnancy affect asthma?

Several physiological changes occur during pregnancy that can affect asthma control. Consequently, during pregnancy the severity of asthma remains stable in approximately a third of women, worsens in another third, and improves in the remaining third.[43] There is also some evidence that the course of asthma is similar in successive pregnancies.[134,135]

At what stage in pregnancy are exacerbations most likely to occur?

If symptoms do worsen, this is most likely to occur in the second and third trimesters.[135] The most severe symptoms usually occur between 24 and 36 weeks of pregnancy.[133] Thereafter, symptoms often decrease significantly in the last four weeks of pregnancy, with 90% of women experiencing no asthma symptoms during labour or delivery.[134]
Pregnant women with moderate/severe asthma should be closely monitored to keep their asthma well controlled.[132]

Does asthma affect pregnancy outcomes?

There is a small but significant increase in pregnancy complications, including a 15 to 20% increased risk of perinatal mortality, pre-eclampsia, preterm delivery and low birth weight infants compared to women without asthma. The risk is greater in women with more severe asthma. However with adequate surveillance and treatment, pregnancy and delivery complications can be avoided.[136] There are no known increased risks of congenital malformations.[130,131]

Safety of drug therapy in pregnancy?

Pregnant women should be managed like any other individual with asthma.[50,85] Good asthma control is important to avoid problems for both mother and baby.[132] Experience with many of the medications used to treat asthma suggest minimal risk for use during pregnancy.[129] The risk of harm to the fetus from severe or chronically under-treated asthma outweighs any small risk from the medications used to control asthma.[132] Therefore advice is to continue the use of all medication as normal in pregnancy, with the exception of leukotriene receptor antagonists. See summary of relative safety of asthma medication in pregnancy in **TABLE ONE**.

Prescribing Notes – Asthma and Pregnancy

- ► Use short acting β2 agonists as normal.[15,132]
- ► Use long acting β2 agonists as normal.[132]
- ► Use inhaled steroids as normal.[15,132]
- ► Use oral and intravenous theophyllines as normal.[132]
- ► Oral steroids should not be withheld in acute severe asthma.[15]
- ► Continue with leukotriene receptor antagonists if they have been started prior to pregnancy and considered essential.[50,132]
- ► As in other settings, long acting β2 agonists should always be used with inhaled steroids.[132]

Drug therapy in breastfeeding

The more established medicines used to treat asthma, including steroid tablets, have been shown to be safe to use in breastfeeding mothers.[152] There is less experience with newer agents.[132] Women with asthma should be encouraged to breastfeed their babies and use asthma medications as normal during breastfeeding in line with the manufacturers'recommendations.[50,132]

Prescribing Notes – Asthma and Breastfeeding

- ► Salbutamol, terbutaline and salmeterol inhalers are considered safe.[14]
- ► Inhaled steroids are safe and oral corticosteroids are considered safe.[14]
- ► Theophylline may cause toxicity in younger infants.[14]
- ► No published evidence of safety of leukotriene receptor antagonists in breast-feeding.[123]
- ► As in other settings, long acting β2 agonists should always be used with inhaled steroids.[132]

TABLE ONE: RELATIVE SAFETY OF ASTHMA MEDICATION IN PREGNANCY

Drug Class	Safety in Pregnancy
β2 Agonists	No significant association has been demonstrated between short-acting β2 agonists and major congenital malformations or adverse perinatal outcome.[128, 141,142-144] Studies have shown no differences in perinatal mortality, congenital abnormalities, prematurity, mean birth weight, Apgar scores or labour/delivery complications.[145] Systematic reviews have shown no increased risk of congenital malformations, pre-term delivery or pre-eclampsia with long-acting β2 agonists.[140]
Steroid Inhalers	A meta-analysis of four studies of inhaled corticosteroid use in pregnancy showed no increase in the rate of major malformations, pre-term delivery, low birth weight or pregnancy-induced hypertension.[151]
Leukotriene receptor antagonists	Leukotriene receptor antagonists should not be *started* in pregnancy, however, if the woman is already taking a leukotriene receptor antagonist and it is considered essential (i.e. demonstrated significant improvement in asthma control with these agents prior to pregnancy not achievable with other medications), continue treatment.[50,132]
Theophyllines	No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to methylxanthines.[128]
Oral corticosteroids	Some studies have found an association between steroid tablet use and pregnancy-induced hypertension or pre-eclampsia, pre-term labour[137] and fetal growth retardation but severe asthma may be a confounding variable.[137] There is much published literature showing that steroid tablets are not teratogenic. However the possibility of an association with oral clefts has not been ruled out as studies have produced conflicting results.[128,138,139] Even if it is real, the benefits of treatment with oral corticosteroids for an acute attack outweigh the potential risks and steroid tablets should never be withheld because of pregnancy.[50,132]

Management of Depression

Depression affects an estimated 15% of women of reproductive age.[153]

What preconceptual care is recommended?

Optimise control of depression before conception with a drug therapy that is suitable for use during pregnancy.

Risks of untreated depression

Uncontrolled depression in pregnancy has been associated with an increased risk of miscarriages, prematurity, and low birthweight.[80] Furthermore, suicide is a leading cause of maternal death in the UK. Inadequate treatment of these conditions is not acceptable.[3,25] Women who abruptly discontinue their antidepressants because of fears of teratogenicity

exhibit higher rates of morbidity and hospitalisation, including suicide ideations and attempts.[156,157]

Effect of pregnancy on antidepressants levels

An increase in body weight (i.e. a decrease in antidepressant dose per kilogram body weight) and increased activity of several cytochrome enzymes can result in lower serum concentrations of some antidepressants. Therefore, some pregnant women may actually need higher doses of antidepressant in late pregnancy. That said, many SSRIs and SNRIs have a flat dose-response curve, i.e. a decrease in levels may not necessarily result in a decreased response.
The lowest dose that is effective should be used; women should be advised to report any change in symptoms to enable a dose change if thought clinically necessary.[78]

Treatment of choice in pregnancy?

Mild to moderate depression may be managed by **psychological therapy** alone if possible.[3] However, if the woman's psychiatric condition necessitates pharmacotherapy, the benefits of drug therapy far outweigh the potential risks to the newborn.[78]

Tricyclic antidepressants have been used in many pregnancies, with seemingly no adverse effects on the fetus, apart from short-lived withdrawal symptoms neonatally.[3] However, **selective serotonin reuptake inhibitors (SSRIs)** are the most widely used class of antidepressant, not only in the general population, but also in pregnant women, because of good documentation of efficacy, relatively few adverse effects, and safety in overdose.[155]

SSRI/SNRI of choice in pregnancy?

Fluoxetine is often preferred as there is more experience with it compared to other SSRIs in pregnancy.[6,44,78]
Paroxetine taken in the first trimester may be associated with fetal heart defects.[44]
Venlafaxine may be associated with increased risk of high blood pressure at high doses, higher toxicity in overdose than SSRIs and some tricyclic antidepressants, and increased difficulty in withdrawal.[44]

Safety of SSRIs / SNRIs in pregnancy?

Four main concerns have been raised in some studies regarding the safety of SSRIs and serotonin noradrenaline reuptake inhibitors (SNRIs) in pregnancy:

1. Congenital malformations
2. Persistent pulmonary hypertension of the newborn (PPHN)
3. Poor neonatal adaptation syndrome
4. Long-term neurobehavioral effects.

See 'Potential obstetric and fetal complications of SSRIs and SNRIs' below for further detail.

MHRA cautions on safety of SSRIs and SNRIs in pregnancy

2005 – Paroxetine: use in first trimester associated with increased risk of congenital (including cardiac) malformations; use in the later stages of pregnancy associated with withdrawal signs in the neonate.[70]
2010 – Fluoxetine: possible small risk of congenital cardiac defects.[69]
2011 – SSRIs and SNRIs: risk of persistent pulmonary hypertension in the newborn.[68]

Potential obstetric and fetal complications of SSRIs and SNRIs

1. Congenital malformations

In 2005 the MHRA issued a safety warning following epidemiological studies that the use of paroxetine in the first trimester was associated with an increase in the risk of birth defects in the newborn from 3% to around 4% for all congenital malformations and from 1% to around 2% for congenital cardiac malformations.[70] Since then, over 30 epidemiological studies examined the association between maternal SSRI use and the development of congenital heart defects.[78] Results have been conflicting, with some showing risk of malformation while others show no risk of malformation with the use of SSRIs in pregnancy.[78]
Ventricular septal defects (VSDs) appear to be the most common cardiac congenital malformation reported with SSRIs.[171] Incidence is difficult to determine given that infants of women with depression are more likely to be investigated for cardiac anomalies (therefore detection is also more likely).[154] Additionally, most muscular-type VSDs tend to close spontaneously in infancy, so unexposed children, if examined later, will not be seen to exhibit the VSD.[78]

2. Persistent pulmonary hypertension of the newborn (PPHN)

A systematic review and meta-analysis reported an increased absolute risk for development of PPHN after exposure to SSRIs in late pregnancy was 2.9 to 3.5 per 1000 infants.[256]
The MHRA recommend close observation of neonates exposed to SSRIs or SNRIs for signs of PPHN after birth.[68] Any advice to reduce or taper off SSRI dose at term should be considered alongside the risks of untreated depression in late pregnancy.[78] See later – 'Should the dose of SSRI/SNRI be reduced close to term?'

3. Poor neonatal adaptation syndrome

This has been reported in 10 to 30% of infants who were exposed at term to SSRIs or SNRIs. Symptoms include jitteriness, poor muscle tone, weak cry, respiratory distress, hypoglycemia, low Apgar scores and seizures.[170] The condition is usually self-limiting, but will necessitate observation of the newborn in hospital for a few days.[159]

4. Long-term neurobehavioral effects

A relatively small number of studies have examined neurocognitive and behavioural outcome after use of SSRIs or SNRIs during pregnancy. These studies have generally been reassuring, failing to show impairment in cognition, learning, or behaviour.[161] They also highlighted the effects of maternal depression itself on child development.[162] In one study investigators were able to separate the effect of depression from treatment by comparing children who had been exposed to venlafaxine in utero with their unexposed siblings and showed no differences in neurocognitive or behavioural achievements.[163]

Should the dose of SSRI/SNRI be reduced close to term?

The practice of gradually discontinuing antidepressants during the third trimester in an attempt to minimise withdrawal effects in the neonate is controversial. This strategy carries a potentially high risk of relapse during the third trimester and early postpartum period and does not rule out the possibility that the baby would experience withdrawal symptoms in utero.[167-169]
Untreated depression in late pregnancy is the

strongest predictor of postpartum depression, which can be life-threatening.[78]

Prescribing Notes – Depression and Pregnancy
► Mild to moderate depression: psychological therapy alone *if possible*.[3]
► If a SSRI is clinically indicated then it should be prescribed.[3]
► A tricyclic antidepressant (imipramine or amitriptyline) may be considered.[3]
► Consultation of the most up to date reference sources is recommended for individual drugs as new data emerges.
► Avoid abrupt discontinuation of antidepressants.[78]

Does the newborn require additional monitoring?
Yes, it is important to monitor the baby for PPHN and poor neonatal adaptation syndrome to allow early initiation of treatment.[78]

Is breastfeeding compatible with antidepressants?
If a mother wishes to breastfeed this should be encouraged, as the numerous nutritional and immunologic advantages of breastfeeding by far outweigh any theoretic risk of antidepressants during breastfeeding.[78] If the baby was exposed to the antidepressant in utero, then the impact of postnatal exposure through milk is much lower.[78]
Few adverse reactions in breastfed infants have been reported. However, all infants should be monitored for drowsiness, poor feeding, irritability, or behavioural effects.[123]

Prescribing Notes – Depression and Breastfeeding
► Sertraline is the SSRI of choice in the breastfeeding mother (shorter half-life and lower passage into milk than other SSRIs).[14]
► Tricyclic antidepressants are probably safe.[14] Check individual drug safety.
There is very limited experience of the safety of monoamine oxidase inhibitors, reboxetine, venlafaxine, mirtazapine, agomelatine and duloxetine in breastfeeding. Therefore these agents are not considered first line antidepressants in breastfeeding women.[257]
► Monitor infants for drowsiness, poor feeding, irritability, or behavioural effects.[123]

Management of Diabetes Mellitus

Management of diabetes mellitus in pregnancy may involve management of women with:
1. Type 1 diabetes (pre-existing) or
2. Type 2 diabetes (pre-existing) or
3. Gestational diabetes.

Prevalence of diabetes in pregnancy?
The prevalence of gestational diabetes and type 2 diabetes in pregnancy has increased markedly in recent years.[184,252] This is in relation to both increased rates of obesity and increased detection of diabetes during pregnancy.[252]

What preconceptual care is recommended?
Pre-pregnancy care provided by a multidisciplinary team is strongly recommended for women with diabetes. The importance of good glycaemic control should be emphasised before conception and throughout pregnancy.[45] A prescription of folic acid is recommended (see point below).[8]

What dose of folic acid should be prescribed?
Women with diabetes who are planning to become pregnant should be advised to take folic acid at a dose of **5mg per day**, until 12 weeks of gestation to reduce the risk of having a baby with a neural tube defect.[45]

Why is it important for women with diabetes to plan their pregnancies?
There is an increased prevalence of congenital anomalies and spontaneous abortions in women with diabetes who are in poor glycaemic control during the period of fetal organogenesis.[182] A woman may not even know she is pregnant at this time. For this reason, pre-pregnancy counselling and planning are essential in women of child-bearing age who have diabetes.[183] Women with poorly controlled diabetes and glycosylated haemoglobin (HbA1c) above 86mmol/moL (or 10%) should be strongly advised to improve diabetic control prior to conception.[6,45]

The importance of good glycaemic control in pregnancy
It is important to establish tight glycaemic control before and during pregnancy.[21] Pre-pregnancy glycaemic control should be maintained as close to the non-diabetic range as possible, taking into account risk of maternal hypoglycaemia.[184] If it is safely achievable, women with diabetes should aim to keep fasting blood glucose between 3.5 and 5.9 mmol/litre and 1-hour postprandial blood glucose below 7.8 mmol/litre during pregnancy.[45]

Self-monitoring of blood glucose in pregnancy
► Women with diabetes should be advised to test before and 1 hour after every meal during pregnancy.[45] This applies to women with type 1, type 2 and gestational diabetes.
► Women with insulin-treated diabetes should be advised to test blood glucose levels before going to bed at night during pregnancy.[45]
► **Pregnant women will therefore need to test their blood glucose levels at least seven times a day.[45] Sufficient test strips should be prescribed to allow this.**

How does pregnancy affect diabetes?[45,172]
- Change in eating pattern. Nausea and vomiting in pregnancy may disrupt normal eating, and changes in timing or dose of insulin may be required.
- Increase in insulin dose requirements. Insulin dose requirements change in pregnancy as a consequence of the physiological increase in insulin resistance. The extent of increase is determined by placental hormones and varies in successive pregnancies in any one woman.[172] The dose of insulin generally needs to be increased in the second and third trimesters of pregnancy.[5] The average increase in insulin requirement is 40%, with a wide range from no change to a higher than three-fold increase.[173]

- Greater importance of tight glucose control (ideally HbA1C < 43mmol/moL (or 6.1%)).
- Increased risk of severe hypoglycaemia and unawareness of hypoglycaemia during pregnancy.
- Risk of deterioration in pre-existing retinopathy – need to assess.
- Risk of deterioration of established nephropathy – need to assess.
- Lower renal threshold for glycosuria.

How does diabetes affect pregnancy?

Diabetes in pregnancy is associated with risks to the woman and to the developing fetus.[45]
Obstetric complications: increased risk of miscarriage, maternal infection, pre-eclampsia, premature labour, polyhydramnios and failure to progress in first or second stage.[184]
Fetal and neonatal complications: congenital malformation, late intrauterine death, fetal distress, hypoglycaemia, respiratory distress syndrome and jaundice.[184] Rates of fetal and neonatal loss and major congenital malformation are increased by at least two to threefold.[184].
See 'Potential obstetric and fetal complications in diabetes' below for further detail.

Potential obstetric and fetal complications in diabetes

1. Congenital malformations

Pre-existing type 1 and type 2 diabetes are associated with an increased risk of congenital malformations. However, studies have not demonstrated an increased malformation rate in infants born to women who develop gestational diabetes.[6]
Hyperglycaemia exerts its teratogenic effects during the period of organogenesis and pregnancy is usually confirmed when much of this time has elapsed.
Diabetes confers a significant increase in risk of early spontaneous fetal loss, often as a consequence of non-viable, severe malformation.[177]
Good glycaemic control during organogenesis is therefore vital to reduce teratogenicity.[6,174,175] Indeed, very poor control of blood glucose can lead to a 25% risk of congenital malformation.[177] This should be balanced against the risk of hypoglycaemic episodes which are associated with significant maternal and fetal risks.

2. Macrosomia

Women with pre-existing or gestational diabetes are at risk of large for gestational age infants and fetal macrosomia (birth weight >4000grams). Macrosomia occurs in about a fifth of pregnancies in women with type 1 diabetes[140] (this is twice the incidence of women without diabetes). There is a subsequent increased risk of birth injury to these babies. Shoulder dystocia occurs in about 8% of births to mothers with diabetes, compared with 3% in the background population.[178,179]
There is also a greater risk of more severe trauma to the mother, with potential future problems of poor pelvic floor function.[8]

3. Pre-eclampsia

Pre-eclampsia is four times more likely to occur in women with type 1 diabetes than in women without diabetes,[180] and even more likely in the presence of nephropathy.[181]

Choice of insulin in pregnancy?

Insulin is safe to use under normal therapeutic conditions in pregnancy and does not cross the placenta.[6]
Isophane insulin (NPH) should remain the basal insulin of choice in pregnancy unless the clinical benefit of a basal insulin analogue has been demonstrated on an individual basis.[45,184]

Safety of insulin analogues in pregnancy?

Evidence of the safety of long-acting insulin analogues in pregnancy is limited, therefore NPH insulin is recommended where longer-acting insulins are needed.
A small randomised controlled trial (RCT) showed non-inferiority of insulin detemir to NPH insulin with respect to efficacy and safety in pregnant women with type 1 diabetes.[227] Therefore insulin detemir may be considered as an option.[5]
Several case control studies suggest no increase in adverse outcomes with glargine.[186-189]
The short-acting insulin analogues (lispro and aspart) appear safe in pregnancy and may be considered in individual patients where hypoglycaemia is problematic.[184]

Can oral anti-diabetic agents be used to manage type 2 diabetes in pregnancy?

Women with type 2 diabetes may be advised to use metformin as an adjunct or alternative to insulin in the pre-conception period and during pregnancy, when the likely benefits from improved glycaemic control outweigh the potential for harm. All other oral hypoglycaemic agents should be discontinued before pregnancy and insulin substituted.[45]
Women with type 2 diabetes inadvertently treated in early pregnancy with a sulfonylurea should be advised that these medications do not appear to carry additional risk of teratogenesis or early pregnancy loss.[184]

Safety of other drugs in the management of type 2 diabetes?

As type 2 diabetes is a cardiovascular disease, women with type 2 diabetes are likely to be taking anti-hypertensives and lipid-regulating drugs.
For choice of antihypertensives in pregnancy, see section on Management of Hypertension.
Statins should be discontinued before pregnancy or as soon as pregnancy is confirmed.[45]

What is gestational diabetes?

Gestational diabetes is defined as glucose intolerance with onset or first recognition during pregnancy.[228]
Gestational diabetes usually occurs in the second and third trimester.[251] Extra insulin requirements are needed during pregnancy – when these are not met, gestational diabetes can occur.[251] Women diagnosed with gestational diabetes in the first trimester will likely have had pre-existing diabetes.[251]

What are the recognised causes or risk factors for developing gestational diabetes?

The cause of gestational diabetes is not completely known, although there seems to be a consensus that hormones produced by the placenta play a major role in the disease.[229]
Risk factors for gestational diabetes include obesity, pregnancy weight gain, age and family history of diabetes.[230,231]

How is gestational diabetes managed?

Most women with gestational diabetes can be managed by changes in diet and exercise.[45] Between 10% and 20% of women will require oral hypoglycaemic agents or insulin therapy if diet and exercise are not effective in controlling gestational diabetes.[45] Metformin or glibenclamide may be considered as initial pharmacological, glucose-lowering treatment in women with gestational diabetes (sulfonylureas other than glibenclamide should not be used in pregnancy due to placental passage).[184]
If blood glucose levels remain in the range for established diabetes, intensive specialist management and initial therapy with insulin is required.[184]

Does gestational diabetes resolve?

Gestational diabetes usually resolves spontaneously after delivery.[6] Women who have been diagnosed with gestational diabetes should discontinue hypoglycaemic treatment immediately after birth.[45] Persisting hyperglycaemia should be excluded before discharge to primary care.[45]
Women who developed gestational diabetes are at increased risk of developing type 2 diabetes in the future. Lifestyle advice should be offered post-natally in the form of weight control, diet and exercise.[45]

Prescribing Notes – Diabetes and Pregnancy

► Insulin requirement changes during pregnancy.[24]
► Start folic acid 5 mg daily before conception and up to 12 weeks thereafter.[23,45]
► Statins are contraindicated.[184]

Insulin and breastfeeding

Women with insulin-treated pre-existing diabetes should reduce their insulin immediately after birth and monitor their blood glucose levels carefully to establish the appropriate dose.[45]
Women with insulin-treated pre-existing diabetes should be informed that they are at increased risk of hypoglycaemia in the postnatal period, especially when breastfeeding, and they should be advised to have a meal or snack available before or during feeds.[45]

Oral hypoglycaemics and breastfeeding

Women with pre-existing type 2 diabetes who are breastfeeding can resume or continue to take metformin and glibenclamide immediately following birth but other oral hypoglycaemic agents should be avoided while breastfeeding.[45]

GLP-1 agonists and breastfeeding

Exenatide may be used while breastfeeding as low levels are anticipated in milk (due to the drug's properties) and is likely to be degraded in the infant's GI tract.[123] The same is expected with liraglutide, although UKDILAS recommend caution due to lack of experience.[123]

Prescribing Notes – Diabetes and Breastfeeding

► Insulin is safe because it does not pass into breast milk.[14]
► Metformin and glibenclamide are probably safe; other oral hypoglycaemics should be avoided.[14,123]
►Exenatide may be used with breastfeeding; caution with liraglutide.[123]
► It would be prudent to observe the infant for signs of hypoglycaemia.
► Statins are not recommended.[123]

Management of Epilepsy

Approximately 3 to 4 in 1000 pregnancies occur in women with active epilepsy;[190,191] 1800 to 2400 children are born to women with epilepsy in the UK each year.[192]

What preconceptual care is recommended?

Good preconceptional control with the antiepileptic medication is important.[43] Drugs used before conception are usually continued during pregnancy.[43]

What dose of folic acid should be prescribed?

Start 5 mg folic acid at least 6 weeks before conception and continue for at least the first trimester.[8]

UK pregnancy epilepsy register

There is a UK study investigating which epilepsy treatments show the lowest risk to a baby's health. The register is run and monitored by Dr Jim Morrow, a Consultant Neurologist at Royal Victoria Hospital in Belfast. This can be accessed at:
http://www.epilepsyandpregnancy.co.uk

Review indication for medication

If the woman has had childhood epilepsy and has now been seizure-free for many years, it may be appropriate to consider dose reduction or withdrawal. However, withdrawal or changing anti-epileptic medication necessitates stopping driving because of potential for seizure relapse, with accompanying repercussions on occupation. The main risk factors for relapse are presence of tonic-clonic and myoclonic seizures and initial difficulty controlling the epilepsy.

Principles of drug review are:

1. Withdraw any unnecessary medication.
2. Use the smallest effective dose.
3. Withdraw drugs with fetal effects and replace with safer drugs if possible.

Can anti-epileptic drugs be stopped before pregnancy?

Although anti-epileptic drugs (AEDs) do carry risks in pregnancy, withdrawal of all AEDs before pregnancy is not a realistic option for most women with epilepsy. Seizures, especially convulsive seizures, are more harmful to the mother and to the fetus than the anti-epileptic drugs.[195]

What about women with epilepsy who present already pregnant?

If the woman presents after conception, AED treatment should not be stopped abruptly.[232] Changing the medication post-conception does not reduce the risk of major malformations because she is either in or past the critical period of organogenesis.[233] It could also lead to loss of seizure control, which could present a greater risk to the fetus than AED exposure.[232] If the woman presents within the first trimester, she should be started on 5mg folic acid daily.

Does pregnancy effect epilepsy?

Seizure frequency increases during pregnancy, in a quarter to a third of women, [225] due to a number of factors including hormone changes, changes in pharmacokinetics of AEDs and poor adherence to treatment (because of concerns about adverse effects on the fetus).[25,88]

Does epilepsy itself pose a risk to the fetus?

It is difficult to disentangle the relative contribution of epilepsy itself, seizure frequency, socioeconomic factors and the teratogenicity of AEDs. Stillbirths and neonatal loss are up to twice as likely among pregnant women with epilepsy (whether or not they take AEDs) compared with those without epilepsy.[43,193] Nevertheless, despite the considerable risk of teratogenicity with AED use in pregnancy, over 90% of pregnancies in women with epilepsy proceed without problem.[194] Most women with epilepsy can expect to have a normal pregnancy and delivery. [91]

Risks associated with poorly controlled epilepsy

Poorly controlled epilepsy is potentially dangerous for the mother and fetus.[16-18] A generalised epileptic seizure is always more dangerous for the fetus than drug treatment, due to risks associated with hypoxia and acidosis. A single, brief tonic-clonic seizure has been shown to cause depression of the fetal heart rate for more than 20 minutes.[200] After generalised tonic-clonic seizures, fetal intracranial haemorrhage, miscarriage, and stillbirth have been reported.[193,201,202] A healthy fetus will withstand hypoxic episodes but they may be life-threatening for a sick fetus.[43] Maternal seizures of all types during the first trimester have been associated with a high malformation rate of 12.3% compared with a malformation rate of 4% for infants of mothers with epilepsy not exposed to seizures during the first trimester.[197] Some studies in children of women with epilepsy have demonstrated an increased risk for cognitive dysfunction if maternal seizures occurred during gestation.[198] The effects of non-convulsive seizures on the developing fetus are less clear.[8]

Risk posed by anti-epileptic drugs?

All AEDs are known to increase the risk of congenital malformations. But the majority of women taking AEDs give birth to healthy babies.[194] AED-exposure increases the risk of:

1) Intrauterine growth retardation
2) Minor congenital anomalies
3) Major congenital malformations
4) Neurodevelopmental delay
5) Problems in the neonatal period
6) Stillbirth.

See 'Potential fetal complications with anti-epileptic drugs' for further detail.

A preference for monotherapy

Multiple drug regimens are associated with an increased risk of malformations. A conservative estimate suggests that AED monotherapy doubles, and polytherapy triples, the risk for major congenital malformations.[97] Indeed the rate of major malformations has been reported to be as high as 25% in infants of women receiving four or more AEDs.[197] Therefore the goal is to establish the best seizure control with the fewest possible number of AEDs prior to pregnancy.[91]

Monotherapy with carbamazepine, phenytoin or phenobarbitone in pregnancy appears to be safe to the development of children exposed in utero.

Potential fetal complications with anti-epileptic drugs

1) Intrauterine growth retardation

Low birth weight babies are up to twice as likely among women taking AEDs than among women in general.[203] Low birth weight babies are particularly associated with AED polytherapy.[204]

2) Minor congenital anomalies

Minor anomalies affect 6 to 20% of infants born to women with epilepsy, which is an approximately two-fold increased rate compared with the general population.[205] Many case reports have suggested a characteristic pattern of minor dysmorphic features in children exposed to AEDs.[206-209] These have included characteristic appearances of the eyes (epicanthal folds, hypertelorism), nose (flat nasal bridge, long philtrum), mouth (microstomia, prominent lower lip), and digits (distal phalangeal hypoplasia and nail hypoplasia).[210,211] Many of the craniofacial anomalies are subtle and are outgrown by the age of 5 years.[212] However, multiple anomalies are sometimes markers of more severe problems such as developmental delay.[213]

3) Major congenital malformations

Major congenital malformations are 2 to 3 times more likely in children of mothers treated with AEDs in pregnancy compared with children in the general population.[192,202,205,214-219] Major congenital malformations most commonly associated with AED exposure include:

- Congenital heart defects
- Orofacial clefts
- Neural tube defects
- Urogenital defects.

4) Neurodevelopmental delay

Studies have found a higher prevalence of neurodevelopmental delay in the first two years of life among children born to mothers with treated epilepsy compared to children in the general population.[220] AED exposure during the last trimester may actually be the most detrimental for cognitive outcome.[222] Evidence is still accruing, but recent investigations suggest that exposure to some AEDs may result in altered cognitive function later in development.[97] See 'Do any AEDs carry a greater risk than others in pregnancy?' for further details on risks with valproate.

5) Problems in the neonatal period

● In neonates exposed in utero to AEDs, features such as jitteriness, hypotonia, hypoglycaemia, apnoeic episodes or seizures are generally recognised to be signs of drug withdrawal.[224]

● Some AEDs (e.g. carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, topiramate) induce hepatic enzymes. Potentially this could lead to vitamin K deficiency and bleeding disorders in the newborn.[223] See later 'What is advised around the time of delivery?' for further details.

6) Stillbirth

Fetal mortality is another increased risk for women with epilepsy. Reported rates of stillbirth (fetal loss at greater than 20 weeks of gestational age) vary between 1.3 to 14% compared with rates of less than 1% for the general population.[176]

Do any AEDs carry a greater risk than others in pregnancy?

Sodium valproate is considered particularly teratogenic (neural tube defects) and studies have shown an increase in the incidence of developmental delay in children born to mothers on valproate. A European review is underway to evaluate all currently available evidence on the association between fetal valproate exposure and neuro-developmental delay or autism spectrum disorder.[226]

Sodium valproate should not be used during pregnancy and in women of childbearing potential unless clearly necessary.[226]

Pharmacokinetic features of AEDs during the pregnancy and postpartum period

Pharmacokinetic features of AEDs change during the pregnancy and postpartum period. During pregnancy, AED concentrations may decrease (due to increased plasma volume). However, the risk of convulsive seizure increases only slightly because the decrease in concentration of freely circulating drug is small. Levels of some AEDs must be monitored and the doses adjusted routinely during pregnancy and after birth.[91] The dose of anti-epileptic drug should be increased near term due to increased risk of seizure during labour.[43]

What about the newer drugs?

The focus of research is currently moving from the first to the second AED generation. Lamotrigine is relatively well studied, and data on other novel AEDs, such as levetiracetam, oxcarbazepine, topiramate, zonisamide, gabapentin and pregabalin, are in progress. Safety issues appear to be favourable for lamotrigine, and preliminary results are also promising for levetiracetam and oxcarbazepine.[86]

What is advised around the time of delivery?

Children born to mothers taking enzyme-inducing AEDs are at an increased risk of haemorrhagic disease of the newborn. It is recommended that all such children be given 1mg of vitamin K parenterally at delivery.[47]

Prescribing Notes – Epilepsy and Pregnancy

► Monotherapy with an AED is the preferred option.
► Folic acid at a dose of 5mg should be started at least 6 weeks before conception and continued for at least the first trimester.[8]
► As research is currently on-going on safety of AEDs in pregnancy, always check the most up-to-date resources to establish safety of individual AEDs.

Is breastfeeding compatible with anti-epileptic drugs?

A decision to breastfeed while taking anti-epileptic drug(s) will depend on the individual drug(s). Up-to-date reference sources should be consulted on each occasion. A summary of the recent evidence is provided in the 'Prescribing Notes – Epilepsy and Breastfeeding' below.

Prescribing Notes – Epilepsy and Breastfeeding

► Phenytoin, carbamazepine and sodium valproate are excreted in breast milk, but are considered safe if drug levels in mother are kept within therapeutic range.
► Breastfeeding should be avoided if taking phenobarbitone, as it can accumulate in the infant resulting in sedation. Withdrawal effects are also possible.
► Lamotrigine may accumulate because of the infants' immature metabolism, so exercise caution.[19]
► Large doses of diazepam may cause somnolence in the newborn because of a high drug concentration in the breast milk.[43]
► There is no information about the effects of newer anti-epileptic drugs such as gabapentin, vigabatrin or levetiracetam.[14]

Management of Hypertension

Hypertensive disorders occur in up to 10% of all pregnancies and remain a leading cause of maternal and perinatal mortality and morbidity.[25,49,234] An estimated 15% of direct obstetric deaths in the UK are attributable to hypertensive disorders.[25]

What preconceptual care is recommended?

Choice of anti-hypertensive should be compatible with pregnancy. Therefore pregnancy planning is important for women with pre-existing hypertension.
Women who are receiving an ACE inhibitor or an angiotensin antagonist or chlorothiazide should be informed that this will need to be stopped if they become pregnant and alternative treatment considered.[46]

Does hypertension affect pregnancy?

Fetal risks are connected with chronic placental insufficiency, e.g. small-for-gestational-age newborn and fetal hypoxia. The maternal risks in very severe hypertension are circulatory brain disturbances, heart failure and complications resulting from superimposed pre-eclampsia.[43]
A slight or moderate rise of arterial blood pressure without proteinuria is not an indication of high risk.
Close monitoring of the pregnancy in the outpatient clinic of the maternity hospital is important. If proteinuria occurs, the expectant mother must be admitted to the hospital.[43]

Does pregnancy affect hypertension?

During the early weeks of normal pregnancy blood pressure falls, reaching its lowest point in the second trimester, then climbing slowly in later pregnancy to reach pre-pregnancy levels at term.[236,237] These changes are related to multiple physiological / environmental factors, and complicate the diagnosis of hypertensive disorders in pregnancy.

Categories of hypertensive disorders in pregnancy

1. Chronic hypertension

Chronic hypertension is hypertension that is present at the booking visit or before 20 weeks or if the woman is already taking antihypertensive medication when referred to maternity services. It can be primary or secondary in aetiology.[46]
Most women with chronic pre-existing hypertension will have mild hypertension in pregnancy. [240]

2. Gestational hypertension
Gestational hypertension is new hypertension presenting after 20 weeks without significant proteinuria and which resolves postpartum.[46,49]

If a woman with chronic or gestational hypertension develops proteinuria after 20 weeks' gestation then her care becomes that of a woman with pre-eclampsia.[49]

3. Pre-eclampsia
Pre-eclampsia is new hypertension presenting after 20 weeks with significant proteinuria.[46]
This is characterised by new-onset proteinuria (or by a sudden increase in the protein level if proteinuria is already present) along with an acute increase in the level of hypertension (assuming proteinuria already exists).[8]

Which anti-hypertensive drugs can be used in pregnancy?
Labetalol is the anti-hypertensive of choice in pregnancy.[46] Methyldopa and nifedipine are alternatives after consideration of the adverse effect profile for the mother and the fetus.[46,49]
Methyldopa has a good safety record as an anti-hypertensive in pregnancy.
Nifedipine is used widely in obstetric practice,[43] although the UK national guidelines advise use only after 20 weeks' gestation.
Less information is available on other beta blockers and other calcium channel blockers.

Which anti-hypertensive drugs should be avoided in pregnancy?
ACE inhibitors and angiotensin antagonists are to be changed to other medication when pregnancy is planned. If a woman presents with pregnancy and is taking an ACE inhibitor or angiotensin antagonist, this should be stopped immediately and an alternative treatment prescribed if necessary.[43,49]
They can increase the risk of fetal malformations, fetal renal dysfunction and oligohydramnios. They also inhibit normal gestational development of the vascular system and can cause fetal growth restriction in second and third trimesters.
Diuretic drugs are generally avoided in pregnancy because decreased plasma volume is associated with chronic hypertension and especially with pre-eclampsia.[43] However, some low-dose thiazide diuretics may be used in the second and third trimester if there is a specific indication.

What level of blood pressure is recommended?
NICE recommend that pregnant women with chronic hypertension should aim to keep blood pressure <150/100 mmHg and that women with gestational diabetes are usually only treated when blood pressure is 150/100 to 159/109mmHg or higher.[46]
However, locally, consultant obstetricians aim for lower BP control and aim to keep BP <140/90mmHg.

There is evidence that there is less risk of severe hypertension developing in pregnant women with chronic hypertension if they have 'tight' control of blood pressure. However a meta-regression of randomized controlled trials (RCTs) has shown that the more that blood pressure is reduced in pregnant women with chronic hypertension, the more the birth weight of their infants is reduced. [49]

What are the risks of pre-eclampsia?
Pre-eclampsia is a significant risk factor in the development of intrauterine growth restriction (IUGR) and prematurity.[255] Pre-eclampsia is associated with increased risks of placental abruption, acute renal failure, cerebrovascular and cardiovascular complications, disseminated intravascular coagulation and maternal death.[239] Consequently, early diagnosis of pre-eclampsia and close observation are imperative.

Delivery of the placenta is the only cure for pre-eclampsia. Anti-hypertensive therapy is used to preserve maternal safety while pregnancy is prolonged (for fetal indications) and during the postnatal period (during which time hypertension often persists for days to weeks, particularly after severe disease).[240]

What is eclampsia?
Eclampsia is a convulsive condition associated with pre-eclampsia.[46] Eclamptic seizures are relatively rare and occur in less than 1% of women with pre-eclampsia.[238]

What factors increase risk of developing pre-eclampsia?
High risk
Women at high risk are those with any of the following:
- Hypertensive disease during a previous pregnancy
- Chronic kidney disease
- Autoimmune disease such as systemic lupus erythematosis or antiphospholipid syndrome
- Type 1 or type 2 diabetes
- Chronic hypertension.

Moderate risk
Factors indicating moderate risk are:
- First pregnancy
- Age 40 years or older
- Pregnancy interval of more than 10 years
- Body mass index (BMI) of 35 kg/m² or more at first visit
- Family history of pre-eclampsia
- Multiple pregnancy.[46]

Symptoms of pre-eclampsia?
Pregnant women should be made aware of the need to seek immediate advice from a healthcare professional if they experience symptoms of pre-eclampsia.

Symptoms include:
- Severe headache
- Problems with vision, such as blurring or flashing before the eyes
- Severe pain just below the ribs
- Vomiting
- Sudden swelling of the face, hands or feet.[46]

Use of low dose aspirin in pregnancy?
NICE recommend that women with one or more high risk factors for pre-eclampsia should be advised to take 75 mg of aspirin daily from 12 weeks until the birth of the baby.[46] Women with two or more moderate risk factor for pre-eclampsia should also be advised to take 75 mg of aspirin daily from 12 weeks until the birth of the baby.
Locally, consultant obstetricians recommend the use of aspirin until around 38 weeks gestation.
In some women, e.g. thrombophilias, it may be advantageous to give aspirin earlier than12 weeks.[254]

The use of aspirin for pre-eclampsia is an unlicensed indication.[49]

Safety of low dose aspirin in pregnancy?

The effects of low-dose aspirin during pregnancy have been studied extensively. There is no good evidence to suggest that low-dose aspirin is associated with an increased risk of fetal toxicity or congenital abnormalities.[49] No increase in bleeding complications, decrease in fetal urine excretion, or significant effects on the ductus arteriosus have been associated with low-dose aspirin.[49]
Dyspepsia is a common adverse effect, and gastroprotection with omeprazole may be needed for women who are at high risk of gastrointestinal ulceration or bleeding.[49]

Prescribing Notes – Hypertension and Pregnancy

► Labetalol is licensed for use in pregnancy and is the anti-hypertensive drug of choice in pregnancy.
► Labetalol should be avoided in patients with asthma
► ACE inhibitors and angiotensin antagonists should be avoided in pregnancy.[5]
► If nifedipine is to be used, prescribe a modified-release preparation (short acting preparations carry risk of rapid hypotension).
► Omeprazole may be co-prescribed with low dose aspirin for gastroprotection.

Choice of anti-hypertensive following birth?

If a woman with pre-existing hypertension has taken methyldopa during pregnancy, stop methyldopa within two days of birth and restart the pre-pregnancy anti-hypertensive treatment (as methyldopa may increase the risk of depression).[46]
For women who develop gestational hypertension, the same anti-hypertensive will be continued postpartum (unless the woman has been taking methyldopa which should be stopped two days postpartum) until her blood pressure has returned to normal or until the woman has been referred to a specialist for a medical review should her blood pressure remain elevated.[49]

Are anti-hypertensive drugs compatible with breastfeeding?

TABLE TWO provides a summary of the current evidence on safety of anti-hypertensive drugs in breastfeeding.

TABLE TWO: Safety of anti-hypertensive drugs in breastfeeding	
Beta blockers	Considered safe but, if maternal dose is high, the infant should be monitored for signs of beta blockade.
Methyldopa	Considered safe but, owing to its potential side effect of low mood, may not be the first choice in the postpartum woman.
Nifedipine and verapamil	Likely to be safe but there are few data available.
ACE inhibitors and angiotensin antagonists	Captopril and enalapril are probably safe. There are few data about other ACE inhibitors and angiotensin antagonists. Avoid in premature and newborn infants.[123]
Amlodipine	Insufficient evidence on the safety.[46]
Diuretics	Avoid if the woman is breastfeeding or expressing milk.[46]

What monitoring should be carried out for breastfed infants?

Assess the clinical wellbeing of the baby, especially for adequacy of feeding, at least daily for the first two days after birth.[46]

Management of Thyroid disorders

HYPOTHYROIDISM

Hypothyroidism, usually characterised by a high thyroid stimulating hormone (TSH) value, occurs in around 2.5% of otherwise normal pregnancies.[241,242]

What preconceptual care is recommended?

Thyroid-stimulating hormone (TSH) and free thyroxine (FT4) levels should be checked before conception if possible, to check adequacy of treatment.[53]
Women receiving treatment for hypothyroidism should be advised to contact their GP as soon as she thinks she may be pregnant.[53] Women should be informed that levothyroxine is not only safe but essential for the baby's development, and not to stop levothyroxine in pregnancy.

Does pregnancy affect hypothyroidism?

Most women will require an increase in their levothyroxine dose to maintain adequate levothyroxine levels and mimic the pregnancy associated fall in thyroid-stimulating hormone seen in the first and second trimesters.[20,39] See 'What levothyroxine dose changes are required during pregnancy?' for further details.

What is drug treatment of choice of hypothyroidism in pregnancy?

Levothyroxine is a naturally occurring thyroid hormone produced by the mother and the fetus. Levothyroxine is compatible with all stages of pregnancy.[246] It is essential that pregnant women with hypothyroidism receive adequate levothyroxine replacement therapy.[245] See 'Prescribing Notes – Thyroid disorders and Pregnancy' for further details.

What levothyroxine dose changes are required during pregnancy?

At confirmation of pregnancy, the dose of levothyroxine should be immediately increased and TSH and FT4 levels checked while waiting for referral to a specialist.[53] The dose of levothyroxine should be increased usually by at least 25 to 50 micrograms levothyroxine.[53] The size of the initial increase in dose will depend on the dose the woman is already taking and the TSH and FT4 concentrations. A 30 to 50% increase may be required. If there is any uncertainty about what dose to prescribe, seek immediate specialist advice so that there is no delay in the woman receiving an adequate dose of levothyroxine.[53]

Do biochemical reference ranges change during pregnancy?

Yes, biochemical diagnosis needs to take into account pregnancy-specific reference ranges for thyroid function tests.[244] The reference range for TSH is lower throughout pregnancy compared with non-pregnant women.[258] Local lab references should be referred to if available. These will be in the range as shown in **TABLE THREE**.

TABLE THREE: Pregnancy-specific reference ranges[245,258]

	Non-pregnant	First trimester	Second trimester	Third trimester
TSH (mIU/L)	0.4 – 4	0.1 – 2.5	0.2 – 3	0.3 – 3
Free T4 (pmol/L)	9 – 25	9 – 25	9 – 25	7.3 – 15.4

How often should thyroid function be monitored in pregnancy?

TSH and FT4 levels should be monitored:

- Every 4 weeks during titration of levothyroxine.
- Every 4 weeks during the first trimester, and again at 16 weeks and at 28 weeks of gestation, in a woman who is on a stable dose of levothyroxine.
    - More frequent tests may be appropriate on specialist advice.[53]

Risks of untreated hypothyroidism?

Untreated or undertreated hypothyroidism is associated with low birth weight secondary to medically indicated preterm delivery, pre-eclampsia, placental abruption and impaired neuropsychological development of the offspring.[246]

Symptoms of hypothyroidism or symptoms of pregnancy?

Recognising hypothyroidism can be difficult during pregnancy, as the signs and symptoms of thyroid disease can be hard to distinguish from features of pregnancy itself (e.g. weight gain, constipation, fatigue). Also, physiological changes in pregnancy will mask some of the features of hypothyroidism (e.g. cold intolerance and bradycardia).[43]

HYPERTHYROIDISM

Hyperthyroidism occurs in 0.2% of all pregnancies. It is usually caused by Graves' disease.[243]

What preconceptual care is recommended?

Specialist referral is required for women currently receiving treatment for hyperthyroidism or with a history of hyperthyroidism. Thyroid function should be checked before conception.[54]
Propylthiouracil is the drug of choice in the first trimester and so should be used preconception also.[5]
Women who have recently received radioiodine treatment should be advised to avoid becoming pregnant for at least 6 months after treatment.[54]

Does pregnancy affect hyperthyroidism?

Hyperthyroidism often improves during pregnancy and anti-thyroid drugs can sometimes be stopped during the third trimester,[42] which lessens the risk of the neonate suffering transient hypothyroidism.

What is the treatment of choice of hyperthyroidism in pregnancy?

If anti-thyroid medication is required, propylthiouracil is preferred to carbimazole in the first trimester.
Carbimazole has (very rarely) been associated with neonatal aplasia cutis (a malformation of the scalp).[41]
However a switch to carbimazole may be considered in the second trimester due to risk of hepatotoxicity with propylthiouracil.[5] Both propylthiouracil and carbimazole cross the placenta and can cause fetal goitre and hypothyroidism, so the lowest effective dose should be used.[5]
Radioisotopes should be avoided in pregnancy.[43]
See 'Prescribing Notes – Thyroid disorders and Pregnancy' for further information.

Are block-replace regimens suitable in pregnancy?

No, 'block-replace' regimens are not suitable for pregnant women, because levothyroxine crosses the placenta less than carbimazole, and fetal goitre and hypothyroidism can occur.[41]

Risks of untreated hyperthyroidism?

Maternal complications include miscarriage, placental abruption, and preterm delivery. Congestive heart failure and thyroid storm may also occur, and the risk of pre-eclampsia is significantly higher in women with poorly controlled hyperthyroidism.[247,248] If high titres of thyroid- stimulating antibodies are present at 36 weeks gestation, there is a high risk of neonatal thyrotoxicosis which, although transient, may cause considerable neonatal morbidity if unrecognised.[249]

Symptoms of hyperthyroidism or symptoms of pregnancy?

The clinical presentation of hyperthyroidism may not be obvious in pregnancy because symptoms of tachycardia, sweating, dyspnoea, and nervousness / irritability are seen in normal pregnancy.[247]

What management is required?

Management of hyperthyroidism should be carried out exclusively in secondary care. However, it is helpful if primary care can check serum free thyroxine, free triiodothyronine, and thyroid-stimulating hormone levels when pregnancy is confirmed, and send the results to the specialist with the referral.[54] Biochemical monitoring is important to reduce the risk of fetal goitre.[43]

Prescribing Notes – Thyroid disorders and Pregnancy

Hypothyroidism

► Levothyroxine is safe and should be continued in pregnancy.

► At confirmation of pregnancy, the dose of levothyroxine should be immediately increased and TSH and FT4 levels checked while waiting for referral to a specialist.[53]

► Certain drugs, especially iron, disturb the absorption of levothyroxine; these medications should be taken at different times.[43]

Hyperthyroidism

► Propylthiouracil is preferred to carbimazole in the first trimester of pregnancy. However, in the second trimester a switch to carbimazole may be considered due to risk of hepatotoxicity with propylthiouracil.[5]

► Block-replace regimens are unsuitable.

Is breastfeeding compatible with drugs used in thyroid disorders?

A summary of the safety of drugs used in thyroid disorders in breastfeeding is provided in 'Prescribing Notes – Thyroid disorders and Breastfeeding'. Neonatal thyroid function tests (TFTs) should be monitored in second week of life. The baby's development should be monitored.[14]

Prescribing Notes – Thyroid disorders and Breastfeeding

Hypothyroidism

► Levothyroxine is safe and should be continued.[14]

Hyperthyroidism

► Carbimazole or propylthiouracil have limited excretion in breast-milk and so may be used in breast-feeding.[5,250]

► Use the lowest effective doses of carbimazole or propylthiouracil.[5]

► There is a theoretical risk of infant thyroid suppression with carbimazole at doses >15 mg/day and propylthiouracil >300 mg.[250]

► Radioactive iodine is contraindicated as it can be taken up by the infant thyroid and cause permanent thyroid damage.[14]

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COMPASS THERAPEUTIC NOTES ASSESSMENT
Management of Chronic Conditions in Pregnancy and Breastfeeding

COMPASS Therapeutic Notes are circulated to GPs, nurses, pharmacists and others in Northern Ireland. Each issue is compiled following the review of approximately 250 papers, journal articles, guidelines and standards documents. They are written in question and answer format, with summary points and recommendations on each topic. They reflect local, national and international guidelines and standards on current best clinical practice. Each issue is reviewed and updated every three years.
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Successful completion of these assessment questions equates with **2 hours** Continuing Professional Development time. Circle your answer TRUE (T) or FALSE (F) for each question. When completed please post this form to the relevant address shown overleaf. Alternatively, you can submit your answers online:

- **Doctors and nurses** should submit their answers at: **www.medicinesni.com**
- **Pharmacists** should submit their answers at: **www.nicpld.org**

1	**In the management of asthma in pregnancy**			
	a	Use of inhaled corticosteroids is not associated with fetal malformations, low birth weight, pre-term delivery or perinatal mortality.	T	F
	b	Some studies have shown that the use of oral corticosteroids has been associated with an increased risk of oral clefts, however studies have produced conflicting results.	T	F
	c	Leukotriene receptor antagonists are considered to be drug of choice in pregnancy	T	F
	d	Short-acting beta-2 agonists are considered to be safe for use in pregnancy.	T	F
2	**In the management of depression in pregnancy**			
	a	Paroxetine is the SSRI of choice in pregnancy.	T	F
	b	Newborns should be monitored for PPHN and poor neonatal adaptation syndrome.	T	F
	c	Uncontrolled depression in pregnancy has been associated with an increased risk of miscarriages, prematurity, and low birthweight.	T	F
	d	SSRI dose should always be tapered close to term.	T	F
3	**In the management of diabetes in pregnancy**			
	a	Pre-pregnancy counselling and planning are essential in women of child-bearing age who have diabetes.	T	F
	b	Risk factors for gestational diabetes include obesity, pregnancy weight gain, age and family history of diabetes.	T	F
	c	Women with diabetes who are planning to become pregnant should be advised to take folic acid at a dose of 5mg per day.	T	F
	d	Women with diabetes will need to test their blood glucose levels at least seven times a day.	T	F
4	**In the management of epilepsy in pregnancy**			
	a	Babies born to mothers with epilepsy are at an increased risk of intrauterine growth retardation, major and minor malformations and neurodevelopmental delay.	T	F
	b	Withdrawal of anti-epileptic medication should be the first-line priority in all pregnant women with epilepsy.	T	F
	c	Use of valproate in pregnancy has been associated with developmental delay and structural abnormalities in the newborn.	T	F
	d	The children born to mothers taking enzyme-inducing AEDs should be given 1milligram of vitamin K parenterally at delivery.	T	F
5	**In the management of hypertension in pregnancy**			
	a	ACE-inhibitors are the drugs of choice for the management of hypertension in pregnancy.	T	F
	b	Diuretics are commonly used for the management of gestational hypertension in pregnancy.	T	F
	c	Type 1 and type 2 diabetes are high risk factors for the development of pre-eclampsia.	T	F
	d	Aspirin lowers the risk of pre-eclampsia.	T	F