COMPASS

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

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Contents

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Glossary	
The Apgar score	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
Polyhydramnios	An excessive amount of amniotic fluid surrounding the fetus
Oligohydramnios	A deficiency of amnionic 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 2 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 under-developed 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
Oral clefts	Cleft lip and cleft palate (known together as oral clefts) are birth defects that occur when a baby's lip or mouth do not form properly during pregnancy
POM	Prescription only medicine

Introduction and Background

Pregnancy

Prescribing in women of child-bearing age

It is estimated that in one-third of births in the UK, pregnancy is unplanned.[1] 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. Likelihood of pregnancy and/or contraception should be considered each time a drug is prescribed to someone of child bearing age. If medication is prescribed, this should be for a drug that is considered low risk in pregnancy.

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.[2,3]
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.[5]

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.[5] Pregnant women tend to perceive their teratogenic risk of medications as significantly higher than the true risk.[7] Indeed some pregnant women avoid taking therapy, even for life-threatening medical conditions.[8]

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).[5] Stopping a drug after week 10, because of concerns about teratogenesis, therefore does not usually reduce the risk substantially.[5]

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.[5] Fetotoxicity can occur anytime between the late first trimester and birth.[5]
An example of fetotoxicity is the association between NSAIDs and premature closure of the ductus arteriosus in the third trimester.[5]

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.[5] 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.[5,6]

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

Many drugs do not have a license for use specifically in pregnant women, reflecting the fact that this group is often excluded from studies.[9] When prescribing medicines to pregnant women that are not licensed for use in pregnancy, informed consent should be obtained and documented.[9]

Prescribing in the absence of evidence

Information on the safety of medicines in pregnancy comes from observational studies, which are of variable quality. This makes it challenging to assess the risks and benefits of medicine use during pregnancy, and clinical judgement is required. There should be a full discussion with the patient, and shared decisions made on an individual patient basis.

Change to FDA pregnancy classification system

US information resources are frequently used in the UK when evaluating the relative safety of medicines in pregnancy and breastfeeding. In 2015, the FDA in the US replaced their pregnancy risk letter categories (e.g. A, B, C, D, X) with a new labelling system, Pregnancy and Lactation Labeling Final Rule (PLLR). The old system had been criticised for being overly simplistic, led to misinformation, and did not adequately address the available information. The new labelling system includes a summary of the risks during pregnancy and lactation, a discussion of the data supporting that summary and relevant information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation. It is hoped that the new labelling system will allow better patient-specific counselling and informed decision making.[10]

Supplements in pregnancy and breastfeeding

Folic acid

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.[11]

Women who are at an increased risk of conceiving a child with a neural tube defect: 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).[11] Risk 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.

Vitamin D

A recommended nutritional intake of 10 micrograms daily of vitamin D is recommended for everyone in the general population aged 4 years and above, including pregnant and lactating women.[12]
NB: Women are encouraged to buy vitamin D and folic acid 400micrograms over the counter. Folic acid at the 5mg strength should however be prescribed.[190,191]

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.[5]
► Absence of data does not imply safety.[5]
► Use drugs that have been used extensively in pregnancy, not new ones.[5]
► 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**.

Breastfeeding

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.[13]

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.[5] 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.[14]
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.[13] 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.[5,13]
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.[13] Indeed, adverse events occur rarely in infants older than six months.[15]

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.[5]

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.[13] Some infant conditions, e.g. metabolic diseases may preclude breastfeeding.[13]

Principles of prescribing in breastfeeding

► While it is *usually* reasonable to continue a medicine that was taken during pregnancy, safety of a medicine in breastfeeding should always be checked.
► Drugs licensed for use in infants do not generally pose a hazard.[13]
► Small molecules get into breast milk more easily than large molecules. For example, heparin is not excreted in breast milk.[5]
► 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.[13,14]
► Infants exposed to drugs via breast milk should be monitored for unusual signs or symptoms.[13]
► Avoid unnecessary drug use and limit use of over-the-counter (OTC) products.[14]
► Avoid long-acting preparations, especially with drugs likely to cause serious side effects (e.g. antipsychotic agents).[14]
► 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.[14]
► 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.[13]

Information resources for medicines in pregnancy and breastfeeding

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

- The UK Teratology Information Service (www.uktis.org/index.html)
- Drugs in pregnancy and lactation, Briggs (subscription through Medicines Complete)*
- UK Drugs in Lactation Advisory Service (UKDILAS) http://www.sps.nhs.uk
- LactMed http://toxnet.nlm.nih.gov *
- BNF https://bnf.nice.org.uk/
- NI Regional Medicines Information Service, Belfast Health and Social Care Trust (weekdays 9am – 5pm, tel 028 9063 2032)

* US resources - therefore the conclusions and recommendations may not be the same as those in the UK due to differences in practice and interpretation in the UK.

Pregnancy and asthma

Asthma is one of the most common medical conditions encountered during pregnancy. At any given time, up to 8 percent of pregnant women have asthma.[16] The majority of women with asthma have normal pregnancies and the risk of complications is small in those with well-controlled asthma.[17]

Pregnant women should be managed in the same was as any other individual with asthma, and should be advised of the importance of continuing their asthma medications (including systemic corticosteroids if applicable).[18]

How does pregnancy affect asthma?

Several physiological changes occur during pregnancy that can affect asthma control. The natural history of asthma during pregnancy is extremely variable.[17] During pregnancy, asthma worsens in about one-third of women, improves in one-third, and remains stable in one-third.[16,17] There is also some evidence that the course of asthma is similar in successive pregnancies.[17,19,20]

At what stage in pregnancy are asthma attacks most likely to occur?

If symptoms do worsen, this is most likely to occur in the second and third trimesters.[21] The most severe symptoms usually occur between 24 and 36 weeks of pregnancy.[21] Thereafter, symptoms often decrease significantly in the last four weeks of pregnancy, with 90% of women experiencing no asthma symptoms during labour or delivery.[20]
Pregnant women with moderate/severe asthma should be closely monitored to keep their asthma well controlled.[17]

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.[17] The risk is greater in women with more severe asthma. However with adequate surveillance and treatment, pregnancy and delivery complications can be avoided.[22] There are no known increased risks of congenital malformations.[23,24]

What pre-conceptual care is recommended?

Pregnancy should be an indication to optimise therapy and maximise lung function in order to reduce the risk of an acute attack.[17,22]

Safety of drug therapy in pregnancy?

Pregnant women should be managed like any other individual with asthma.[17] Good asthma control is important to avoid problems for both mother and baby.[17] Experience with many of the medications used to treat asthma suggest minimal risk for use during pregnancy.[17] 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.[17] Therefore advice is to continue the use of all medication as normal in pregnancy. See summary of relative safety of asthma medication in pregnancy in **TABLE ONE**.

TABLE ONE: Relative safety of asthma medication in pregnancy

Drug class	Safety in pregnancy
Short-acting bronchodilators (SABAs) and Long-acting bronchodilators (LABAs)	No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to short-acting β2 agonists.[17,25-29] Studies have shown no differences in perinatal mortality, congenital abnormalities, prematurity, mean birth weight, Apgar scores or labour/delivery complications between pregnant women taking a bronchodilator and control participants.[17,30] Evidence from prescription event monitoring suggests that salmeterol is safe in pregnancy and although there are some data on formoterol, numbers are small. Studies have shown no increased risk of congenital malformations, pre-term delivery or pre-eclampsia with LABAs.[17,31-33]
Steroid Inhalers	No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to ICS.[17,25,27,33-42] A meta-analysis of four studies of ICS use in pregnancy showed no increase in the rate of major malformations, pre-term delivery, low birth weight or pregnancy-induced hypertension.[17,43]
Leukotriene receptor antagonists (LTRAs)	Data regarding the safety of LTRAs in pregnancy are limited.[17] Available studies have shown no increased risk of congenital malformations or pre-term delivery in exposed women.[17] If leukotriene receptor antagonists are required to achieve adequate control of asthma then they should not be withheld during pregnancy.[17,44-47]
Theophyllines	No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to methylxanthines.[17,25,48] For women requiring theophylline to maintain asthma control, measurement of theophylline levels is recommended. Since protein binding decreases in pregnancy, resulting in increased free drug levels, a lower therapeutic range is probably appropriate.[17,49] Therefore, specialist advice should be sought regarding theophylline dosing when prescribing in pregnancy.
Oral corticosteroids	There is much published literature showing that steroid tablets are not teratogenic.[17,25,50,51] However there is a slight concern that they may be associated with oral clefts.[17] Studies have produced conflicting results.[17,27,51-55] The association is therefore not definite and even if it is real, the benefit to the mother and the fetus of steroids for treating a life-threatening disease justify the use of steroids in pregnancy.[17,56,57] Prednisolone is extensively metabolised by placental enzymes so only 10% reaches the fetus, making this the oral steroid of choice to treat maternal asthma in pregnancy.[17]

Prescribing notes — Asthma and Pregnancy

► Use short acting β2 agonists as normal.[17]
► Use long acting β2 agonists as normal.[17]
► Use inhaled steroids as normal.[17]
► Use oral and intravenous theophyllines as normal. Check blood levels of theophylline in pregnant women with acute severe asthma and in those critically dependent on therapeutic theophylline levels.[17] Specialist advice should be sought regarding theophylline dosing when prescribing in pregnancy
► Oral steroids should not be withheld in acute severe asthma. Women should be advised that the benefits of treatment with oral steroids outweigh the risks.[17]
► If leukotriene receptor antagonists are required to achieve adequate control of asthma then they should not be withheld during pregnancy.[17]
► As in other settings, long acting β2 agonists should always be used with inhaled steroids.[17]

Breastfeeding and asthma

Safety of 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.[17] There is less experience with newer agents.[17] Women with asthma should be encouraged to breastfeed their babies and use asthma medications as normal during breastfeeding in line with the manufacturers' recommendations.[17,18]

Prescribing notes — Asthma and Breastfeeding

► Salbutamol, terbutaline and salmeterol inhalers are considered safe.[14,17,58]
► Inhaled steroids are safe and oral corticosteroids are considered safe.[14,17,58]
► Theophylline may cause toxicity in younger infants.[58] Specialist advice should be sought regarding theophylline dosing when prescribing when breastfeeding.
► There is very limited published evidence of safety of leukotriene receptor antagonists. Very low levels of montelukast appear in breastmilk, therefore amounts ingested by the infant would not be expected to cause any adverse effects in breastfed infants. No special precautions are therefore required.[58]
► As in other settings, long acting β2 agonists should always be used with inhaled steroids.[17]

Management of Depression

Pregnancy and depression

Depression during pregnancy is common, and can affect up to 20% of women.[59] Untreated or undertreated depression is associated with adverse effects for both mother and baby. However, many women are not prescribed or do not take antidepressant medicines during pregnancy due to fears surrounding the safety of these medicines in pregnancy.[60] Much of this fear is due to conflicting reports in the literature of safety of antidepressants in pregnancy: while some studies report adverse effects, this is balanced by studies not showing adverse fetal effects.[61] Furthermore, differentiating effects due to antidepressant from effects due to maternal disease is difficult.[62] Perinatal suicides have been associated with lack of active treatment of depression.[63] Inadequate treatment during this time is not acceptable.[64]

Unfortunately, there are no risk-free decisions for pregnant women with depression.[65] The risks and benefits should be discussed with the woman and an informed decision should be made on an individual basis.[66]

Effect of depression on pregnancy outcomes?

Depression during pregnancy has been associated with an increased risk of miscarriages, premature birth, low birth weight, fetal growth restriction and postnatal complications.[59,60,67]

What is the treatment of choice in pregnancy?

Mild to moderate depression may be managed by **non-pharmacological therapy** such as psychotherapy (interpersonal therapy (IPT) or cognitive behaviour therapy (CBT)), exercise, yoga and mindfulness alone if possible.[65]

However, if the woman's psychiatric condition necessitates pharmacotherapy, the benefits of drug therapy far outweigh the potential risks to the newborn.[68] The NICE Clinical Guideline CG192 *Antenatal and postnatal mental health: clinical management and service guidance* advises that, when choosing an antidepressant, take into account:

- the woman's previous response to these drugs
- the stage of pregnancy
- what is known about the reproductive safety of these drugs
- the uncertainty about whether any increased risk to the fetus and other problems for the woman or baby can be attributed directly to these drugs or may be caused by other factors
- the risk of discontinuation symptoms in the woman and neonatal adaptation syndrome in the baby with most antidepressants, in particular paroxetine and venlafaxine.[69]

What is the antidepressant of choice in pregnancy?

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.[72] It remains uncertain as to whether fetal or neonatal effects differ substantially for individual SSRIs, and changing from one SSRI to another in pregnancy on the basis of teratogenic concern is therefore not currently

recommended.[6]

For women with no previous antidepressant use: any SSRI is a reasonable first choice, with the possible exception of paroxetine owing to its higher risk of neonatal adaptation syndrome and withdrawal symptoms in the mother.[70,71]

For women with a history of depression: switching antidepressants during pregnancy or lactation is not recommended (even with paroxetine) as there is no clear evidence that the safety profile of one drug is superior to that of another, and switching from an effective drug could increase the risk of relapse.[66]

Potential obstetric and fetal complications of SSRIs and SNRIs

There are a number of potential complications:

1) Congenital malformations

Data is conflicting on the safety of SSRIs in pregnancy. Several large reviews have shown no specific pattern of major malformations in women taking SSRIs during pregnancy.[66,74,75] However, some studies have shown an increase in both cardiac malformations and septal heart effects (although most studies report this as not clinically significant).[65]

Early studies reported a small absolute increased risk for cardiovascular malformations with SSRIs, especially with paroxetine. The MHRA subsequently issued a warning in 2005 regarding a higher risk of congenital malformations, including cardiac malformations.[77] In 2011, the MHRA released a warning that fluoxetine may be associated with this risk.[78] It should be noted that the naturally occurring incidence of heart defects is 1 per 100 pregnancies: the use of fluoxetine or paroxetine in early pregnancy may increase this risk to 2 in 100.

More recent studies however do not support this association.[76]

Although the data are conflicting, the majority of studies have found no significant increased risk of congenital heart malformations following exposure to SSRIs during pregnancy other than for paroxetine.[60,76]

2) Low birth weight / preterm birth

Pre-term birth has been associated with exposure to antidepressants in the second and third trimesters.[79-81] This is likely to be an effect of the antidepressant rather than maternal depression, as this effect was found to be significant in comparison to depressed mothers who did not take antidepressants.[60] Overall, however, it is thought that pregnancy may be shortened by 3 to 5 days, which is unlikely to be clinically significant.[60,65]

The use of antidepressants has been associated with reductions in birth weight.[81] However, a recent study showed that women with untreated depression delivered infants with significantly lower birth weight compared to women taking an antidepressant.[82]

3) Persistent pulmonary hypertension of the newborn

Persistent pulmonary hypertension of the newborn (PPHN) occurs when the circulatory transition that should occur after birth does not take place. As a result, pulmonary blood vessels do not open up properly, so the pressure inside them remains high.

PPHN presents as severe hypoxaemia due to pulmonary artery hypertension.[83]

PPHN has been associated with the use of SSRIs in late pregnancy.[60] The MHRA issued a warning in 2010, advising that the observed increase in risk is about an extra 3 to 4 cases of PPHN per 1000 pregnancies, and that neonates exposed to SSRIs and SNRIs should be closely observed of for signs of PPHN.[83]

It's worth noting that other risk factors for PPHN, such as obesity, C-section and pre-term delivery, were not controlled for in most studies.[60,84]

4) Poor neonatal adaptation syndrome (PNAS)

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.[85] The condition is usually self-limiting, but will necessitate observation of the newborn in hospital for a few days.[86]

5) Long term behavioural effects

A recent systematic review of prenatal exposure to antidepressants and developmental outcomes reported inconsistent findings.[65,87] Some studies suggest delayed motor development and motor control, and possibly delayed language, but no studies have reported a significant association with cognitive problems.[65,88]

Many studies have also highlighted the effects of maternal depression itself on child development.[60,65]

Data is inconsistent with regards an association between maternal use of antidepressants and the development of autism or autism spectrum disorder (ASD).[60] With much of the research, it is difficult to differentiate between the effects of antidepressant use during pregnancy and maternal-child genetic susceptibility or postnatal environmental factors such as maternal depression.[89]

Should a lower dose of antidepressant be used in pregnancy?

The lowest effective dose should be used. However, suboptimal dosing exposes the woman and the fetus to both the medication and the effects of untreated depression.[60] The aim of treatment should be to achieve complete remission of symptoms.[66]

Due to pregnancy-related changes in absorption, distribution, metabolism, and elimination, an increase in antidepressant dosage is often indicated to maintain a therapeutic effect.[73] 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. Women should be advised to report any change in symptoms to enable a dose change if thought clinically necessary.[68]

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

There is no evidence that tapering the dose of antidepressant prior to expected delivery lessens PNAS, and this strategy could increase the risk of postnatal depression.[67]

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.[68]

Prescribing notes — Depression and Pregnancy

► Mild to moderate depression: psychological therapy alone *if possible*.[3]

► If an antidepressant is clinically indicated then it should be prescribed.[3]

► Consultation of the most up to date reference sources is recommended for individual drugs.

► Avoid abrupt discontinuation of antidepressants.[68]

Breastfeeding and depression

Is breastfeeding compatible with antidepressants?

SSRIs are the antidepressant group for which the most data exist for use in lactation.[93] SSRIs are considered compatible with breastfeeding as exposure to medication through breastfeeding is considerably lower than through placental transfer during pregnancy.[60,66,90]
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.[68]

Does the age of the infant matter?

Yes, higher concentrations are usually seen in infants younger than 3 to 4 months,[91] with the majority of adverse effects seen in infants under 2 months, and very few adverse effects in those older than 6 months.[60,92 94]
Premature infants and those with respiratory depression should not be exposed to SSRIs via breast milk.[93]

What is the antidepressant of choice in breastfeeding?

Sertraline or paroxetine are the preferred SSRIs for use in lactation due to shorter half lives, lower passage into milk and larger pools of data.[93]
Fluoxetine and citalopram have a longer half life, potentially leading to drug accumulation in the infant and an increased risk of side effects. They are best avoided in neonates (due to reduced excretory function). [93,94,97]
Owing to a lack of safety information, other antidepressants such as mirtazapine, duloxetine, venlafaxine, are not considered first line antidepressants during breastfeeding.[96]

Should a different antidepressant be prescribed in breastfeeding to pregnancy?

No, if a woman has been successfully treated with a SSRI in pregnancy and needs to continue therapy after delivery, there is no need to change the drug, provided the infant is full term, healthy and can be adequately monitored.[66,93,99]

Is monitoring of the infant required?

It may be difficult to distinguish, in the short term, between neonatal withdrawal symptoms following in utero exposure and exposure to the drug via breast milk: some symptoms overlap such as agitation, jitteriness, hypotonia and gastrointestinal symptoms. However, sedation has only been reported after drug exposure via breast milk.[93,95] Infants should be monitored for sedation, poor feeding and behavioural effects.[93]

Prescribing notes — Depression and Breastfeeding

► Sertraline or paroxetine are the preferred choices.[93]
► There is no need to change from a drug that a woman is stabilised on, provided the infant is full term, healthy and can be adequately monitored.[66,93,99]
► Monitor infants for drowsiness, poor feeding, irritability, or behavioural effects.[93]

Management of Diabetes

This section will deal with women with **type 1** and **type 2 diabetes**, as well as women who develop diabetes during pregnancy (**gestational diabetes**).

Pregnancy and diabetes

What is the prevalence of diabetes in pregnancy?

Up to 5% of women who give birth in the UK each year have either pre-existing diabetes or gestational diabetes.[100] Of women who have diabetes during pregnancy, approximately 87.5% have gestational diabetes (which may or may not resolve after pregnancy), 7.5% have type 1 diabetes, and 5% have type 2 diabetes.
The prevalence of type 1 diabetes, and especially type 2 diabetes, has increased in recent years. The incidence of gestational diabetes is also increasing as a result of higher rates of obesity in the general population and more pregnancies in older women.[100]

What is gestational diabetes?

Gestational diabetes is defined as glucose intolerance with onset or first recognition during pregnancy.[106]
Gestational diabetes usually occurs in the second and third trimester.[107] Extra insulin requirements are needed during pregnancy – when these are not met, gestational diabetes can occur.[107] Women diagnosed with gestational diabetes in the first trimester will likely have had pre-existing diabetes.[107]

Effect of diabetes on pregnancy outcomes?

Diabetes in pregnancy is associated with risks to the woman and to the developing fetus.[100]
Obstetric complications: miscarriage, pre-eclampsia and preterm labour are more common in women with pre-existing diabetes.[100]
Fetal and neonatal complications: stillbirth, congenital malformations, macrosomia, birth injury, perinatal mortality and postnatal adaptation problems (such as hypoglycaemia) are more common in babies born to women with pre-existing diabetes.[100]

What are the risks with 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[109] (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.[110,111]There is also a greater risk of more severe trauma to the mother, with potential future problems of poor pelvic floor function.[108]

Are women with gestational diabetes at a similar risk to those with pre-existing diabetes?

Studies have not demonstrated an increased

malformation rate in infants born to women who develop gestational diabetes.[6] However, women with gestational diabetes are at a similar risk of large for gestational age infants, fetal macrosomia and increased perinatal mortality.[6]

How does pregnancy affect diabetes and its management?

- **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.[101] The dose of insulin generally needs to be increased in the second and third trimesters of pregnancy.[102] The average increase in insulin requirement is 40%, with a wide range from no change to greater than a three-fold increase.[103]
- **Greater importance of tight glucose control** (ideally HbA1C < 48mmol/moL (6.5%)).[100]
- **Increased risk of severe hypoglycaemia and unawareness** of hypoglycaemia during pregnancy.
- **Diabetic retinopathy can worsen** rapidly during pregnancy — need to assess.[100]
- **Risk of deterioration of established nephropathy** – need to assess.
- **Lower renal threshold for glycosuria**.

What preconception care is needed?

The importance of good glycaemic control should be emphasised before conception and throughout pregnancy.[100]

A prescription of folic acid is recommended. 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.[100] Note: the 5mg strength is a POM, and therefore a prescription is required.

Why is it important for women with diabetes to plan their pregnancies?

Studies have shown an increased risk of congenital malformations in those pregnancies with poor glycaemic control when compared with optimal glycaemic control in the first trimester.[104]

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.[105] Women with poorly controlled diabetes and glycosylated haemoglobin (HbA1c) above 86mmol/moL (10%) should be strongly advised to improve diabetic control prior to conception.[6,100]

What are the recommended blood glucose levels?

It is important to establish good blood glucose control before conception and to continue this throughout pregnancy.[100]

Target blood glucose and HbA1c levels in the preconception period: aim for the same capillary plasma glucose target ranges as recommended for all people with type 1 diabetes, i.e. a fasting plasma glucose level of 5–7 mmol/litre on waking and a plasma glucose level of 4–7 mmol/litre before meals at other times of the day.[100]

Target blood glucose and HbA1c levels during pregnancy: aim for capillary plasma glucose below a fasting levels of 5.3mmol/litre and 1 hour after meals of 7.8mmol/litre or 2 hours after meals of 6.4mmol/litre. Women who are on insulin or glibenclamide should maintain their capillary plasma glucose level above 4 mmol/litre.[100]

Self-monitoring of blood glucose in pregnancy

NICE recommend that pregnant women with diabetes should test their blood glucose levels as follows:

Type 1 diabetes

Test fasting, pre-meal, 1-hour post-meal and bedtime blood glucose levels daily.

Type 2 diabetes or gestational diabetes who are on a multiple daily insulin injection regimen

Test fasting, pre-meal, 1-hour post-meal and bedtime blood glucose levels daily.

Type 2 diabetes or gestational diabetes

Test fasting and 1-hour post-meal blood glucose levels daily if they are:

- on diet and exercise therapy or
- taking oral therapy (with or without diet and exercise therapy) or single-dose intermediate-acting or long-acting insulin.[100]

In practice, local specialists often advise that all pregnant ladies with diabetes monitor fasting sugars, pre and post meals and again at bedtime, regardless of type of diabetes or treatment

A sufficient quantity of test strips should be prescribed to enable self-monitoring.

What is the role of low dose aspirin in diabetes?

Low dose aspirin 75mg is recommended by NICE from 12 weeks gestation for ladies at risk of pre-eclampsia (see later section: Hypertension). Pre-existing type 1 or 2 diabetes are recognised as high risk factors. Specialists in secondary care will start all ladies with pre-existing diabetes on aspirin unless there is a contra-indication.

How is gestational diabetes managed?

For women with a fasting plasma glucose of below 7mmol/l at diagnosis:

- A trial of diet and exercise should be offered in the first instance.[100]
- If blood glucose targets are not met using changes in diet and exercise within 1 to 2 weeks, metformin should be offered.[100] Insulin may be offered at this stage if metformin is contraindicated or unacceptable to the woman.[100]
- If blood glucose targets are not met on diet, exercise and metformin, the addition of insulin to these treatments should be offered.[100]

For women with a fasting plasma glucose above 7mmol/l at diagnosis:

Immediate treatment with insulin, with or without metformin, as well as changes in diet and exercise, should be offered.[100]

For women with a fasting plasma glucose level of 6.0 to 6.9 mmol/litre and who have complications such as macrosomia or hydramnios:

Insulin, with or without metformin, as well as change in diet and exercise should be considered.[100]

Glibenclamide may be considered in women with gestational diabetes:

- in whom blood glucose targets are not achieved with metformin but who decline insulin therapy or
- who cannot tolerate metformin.[100]

TABLE TWO: Relative safety of diabetes medication in pregnancy

Drug class	Safety in pregnancy
Insulin	Insulin is safe to use under normal therapeutic conditions in pregnancy and does not cross the placenta. Adverse outcomes reported for diabetic pregnancies are thought to be related to glycaemic control, rather than a direct consequence of exposure to insulin.[6] No significant differences in fetal or maternal outcomes were found between analogue and regular insulin in recent studies.[6,112-116]
Oral antidiabetic drugs	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.[100]
ACE inhibitors	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*.[100]
Statins	Statins should be discontinued before pregnancy or as soon as pregnancy is confirmed.[100]

Prescribing notes — Diabetes and Pregnancy

► The dose of insulin generally needs to be increased in the second and third trimesters of pregnancy.[102]

► Prescribe folic acid 5 mg daily before conception and up to 12 weeks thereafter.[100]

► Statins should be discontinued before pregnancy or as soon as pregnancy is confirmed.[100]

► Insulin is safe to use under normal therapeutic conditions in pregnancy.[6]

► Metformin is the oral anti-diabetic of choice in type 2 diabetes, all other oral anti-diabetics should be discontinued, and insulin substituted.[100]

Breastfeeding and diabetes

Information is summarised in **TABLE THREE**.

TABLE THREE: Relative safety of diabetes medication in breastfeeding

Drug class	Safety in breastfeeding
Insulin	Insulin is a normal component of breast-milk and is likely to be degraded in the infant's gastrointestinal (GI) tract.[14] 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.[100] 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.[100]
Oral antidiabetic drugs	Women with pre-existing type 2 diabetes who are breastfeeding can resume or continue to take metformin and glibenclamide immediately after birth, but should avoid other oral blood glucose-lowering agents while breastfeeding.[100] There is limited information on safety of exenatide and liraglutide in breastfeeding, but low levels are expected in the milk due to the drugs' properties and both drugs are likely to be degraded in the infant's GI tract.[14]
ACE inhibitors	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 breastfeeding, see section on *Management of Hypertension*.[100]
Statins	Statins are not recommended during breastfeeding due to their potential serious adverse effects in adults, which, theoretically, could occur in the infant.[14,100]

Prescribing notes — Diabetes and Breastfeeding

► Insulin is safe in breastfeeding for the infant.

► Metformin and glibenclamide appear to be compatible with breastfeeding.

► Less information on safety of other oral antidiabetic drugs in breastfeeding is available. Refer to information resources for safety of specific agents in breastfeeding.

► Statins are not recommended during breastfeeding.

Pregnancy and epilepsy

What is the prevalence of epilepsy in pregnancy?

Epilepsy is one of the most common neurological conditions in pregnancy, with a prevalence of 0.5 to 1%.[117] An estimated 2500 infants are born to women with epilepsy every year in the UK.[118]

The 2014 Confidential Enquiries into Maternal Deaths and Morbidity report (MBRRACE-UK) found that fourteen maternal deaths that occurred between 2009 and 2012 were attributed to epilepsy. Twelve of these deaths were classified as SUDEP (sudden unexpected death in epilepsy), with poorly controlled seizures being the main contributory factor.[119]

What pre-conceptual care is recommended?

Pre-conception counselling is essential as careful planning and management of pregnancy can increase the odds of a favorable outcome for women with epilepsy.[120] Benefits of pre-conception counselling include an analysis of treatment plans based upon the most recent evidence, an opportunity to modify anti-epileptic drug (AED) regimens to the safest possible combinations using the lowest effective dose of as few AEDs as possible.[119]

Withdrawal of all AED therapy is not a realistic option for most women with epilepsy. The possibility of status epilepticus and SUDEP should be discussed with all women who plan to stop AED therapy.[121]

The relative benefits and risks of adjusting medication should be discussed with the woman to enable her to make an informed decision. Where appropriate, the woman's specialist should be consulted.[121]

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.

What dose of folic acid should be prescribed?

All women taking AEDs should be offered **5mg per day of folic acid** before any possibility of pregnancy, until at least the end of the first trimester to reduce the incidence of major congenital malformation.[118,121]

UK pregnancy epilepsy register

The UK Epilepsy and Pregnancy Register is a study investigating which epilepsy treatments show the lowest risk to a baby's health. The register is run by the Department of Neurology in the Royal Victoria Hospital (Belfast Trust).
NICE recommend that all pregnant women with epilepsy should be encouraged to notify their pregnancy, or allow their clinician to notify the pregnancy, to this register: http://www.epilepsyandpregnancy.co.uk

What about women with epilepsy who present already pregnant?

Women with epilepsy who become unexpectedly pregnant should be referred urgently to a specialist.[118]
If the woman presents after conception, AED treatment should not be stopped abruptly.[122] 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.[123] It could also lead to loss of seizure control, which could present a greater risk to the fetus than AED exposure.[122] If the woman presents within the first trimester, she should be started on 5mg folic acid daily.

What is the effect of pregnancy on seizure control in women with epilepsy?

Two-thirds of women with epilepsy will not experience a seizure during pregnancy.[118]
The seizure-free duration is the most important factor in determining the woman's risk of seizure during pregnancy.[125] In women who were seizure free for at least 9 months to 1 year prior to pregnancy, 74 to 92% continued to be seizure free in pregnancy.[118,125-127]
Pregnant women who have experienced seizures in the year prior to conception require close monitoring of their epilepsy.[118]
Change to seizure control during pregnancy, is likely 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).[128]

Do pharmacokinetic features of AEDs change during the pregnancy and postpartum period?

During pregnancy, AED concentrations tend to decrease (due to increased plasma volume), especially for lamotrigine and levetiracetam.[135-138] However, the clinical consequences of this in terms of seizure control are difficult to predict.[135]
The dose of lamotrigine may however need to be increased during pregnancy. To avoid neurotoxicity, the dose should be reduced early after birth.[135]

Current practice in AED monitoring is either regular therapeutic drug monitoring [130] or monitoring based on clinical features to adjust the AED dose.[121,131] For most women with epilepsy, routine monitoring of AED concentrations is not indicated. However, measurement of AED concentrations can be useful for adjustment of phenytoin dose, assessment of AED adherence and suspected AED toxicity.[135] The interpretation of AED blood levels is best performed by an epilepsy specialist.[135]

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.

The effect of maternal epilepsy on fetal and infant outcomes is unclear and data from studies are inconsistent.[135] Poorly controlled epilepsy is potentially dangerous for the mother and fetus.[139,140] The long term effect of maternal seizures on the fetus is not well established, although in theory the associated hypoxia and acidosis could adversely affect fetal outcomes, particularly if seizures are frequent and prolonged.[135]

Women with epilepsy are at increased risk for a range of perinatal complications compared with the general population, including preeclampsia, preterm labour, and fetal and maternal mortality.[120,124]Despite this, over 90 percent of women with epilepsy have a normal pregnancy.[118]

What is the risk of congenital malformations due to AEDs?

Women with epilepsy are more likely than women without epilepsy to give birth to children with congenital malformations.[118,141-147] Untreated epilepsy does not appear to be associated with an increased risk of congenital malformations.[118,135,148]

The risk of congenital abnormalities in the fetus is dependent on the type, number and dose of AEDs.[118]

The most common major congenital malformations associated with AEDs are neural tube defects, congenital heart disorders, urinary tract and skeletal abnormalities and cleft palate.[132-134]

For women with a previous child with a major congenital malformation, the risk of recurrence for major congenital malformation is increased (16.8 per 100).[135]

Safety of individual AEDs

The overall risk of major congenital malformation in the general population is approximately 2%.[135] Rates of major congenital malformations vary from study to study, so it is difficult to make comparisons between AEDs. However, rates are consistently higher in studies with sodium valproate.[135]

SIGN (2015) guideline on *Diagnosis and management of epilepsy in adults* has summarised the absolute risk of major congenital malformation risks with AED monotherapy as follows:[135,152]

- Sodium valproate — 6.2% to 11.3%
- Carbamazepine — 2.2% to 5.2%
- Phenytoin — 2.9% to 7.4%
- Lamotrigine — 1.9% to 5.4%
- Gabapentin — 4.1%
- Topiramate — 3.1% to 4.8%
- Levetiracetam — 0.0% to 0.7%

MHRA Warning: Valproate and risk of abnormal pregnancy outcomes

Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and/or congenital malformations (in approximately 10% of cases).

Given these risks, valproate for the treatment of epilepsy or bipolar disorder should not be used during pregnancy and in women of child-bearing potential unless clearly necessary, i.e. in situations where other treatments are ineffective or not tolerated.

New communication materials have been made available to support discussion of these risks with women of childbearing potential and girls who take valproate and can be accessed at: https://www.gov.uk/drug-safety-update/valproate-and-of-risk-of-abnormal-pregnancy-outcomes-new-communication-materials

The risk of major congenital malformation for newer AEDs in monotherapy such as eslicarbazepine, gabapentin, lacosamide, oxcarbazepine, perampanel, pregabalin, topiramate or zonisamide is unknown.[118,135]

Dose of AEDs and risk of adverse effects

For lamotrigine, sodium valproate and carbamazepine montherapies, there appears to be an increased risk of teratogenicity associated with an increased dose.[135,149-151]

Number of AEDs / a preference for monotherapy

Polytherapy carries a much higher risk of major congenital malformations than monotherapy. A conservative estimate suggests that AED monotherapy doubles, and polytherapy triples, the risk for major congenital malformations.[153] Indeed the rate of major malformations has been reported to be as high as 24% in infants of women receiving four or more AEDs.[135]

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.[121,135]

What is advised after birth with respect to AEDs?

Following delivery, blood levels of AEDs may rise, potentially leading to toxicity. A reduction in dose at this time may be advised.[135].

After the birth a review of the mother's AED therapy should be undertaken.[135]

Prescribing notes — Epilepsy and Pregnancy

► No antiepileptic drug should be discontinued during pregnancy unless this has been discussed with an epilepsy specialist.[135]

► Wherever possible sodium valproate should be avoided during pregnancy.[135]

►Folic acid at a dose of 5mg per day before any possibility of pregnancy, until at least the end of the first trimester is recommended.[118,121]

Breastfeeding and epilepsy

Is breastfeeding compatible with AEDs?

All mothers should be encouraged to breastfeed and receive support from their health visitor, midwife and GP.[135] Although AEDs pass into breast milk at varying levels, there is no consistent evidence to show accumulation of any AED in breastfed newborn of women with epilepsy.[135]

Choice will depend on clinical condition, and should primarily be based on suitability for the patient, rather than safety during breastfeeding.[155]

Combination therapy may pose an increased risk to the infant, especially when adverse effects, such as drowsiness, are additive.[155]

Breastfeeding and subsequent weaning usually allow for a gradual withdrawal with usually no adverse sequelae for the infant.[135]Withdrawal effects may occur in infants if a mother suddenly stops breastfeeding, particularly if she is taking phenobarbital, primidone, or lamotrigine.[155]

Close monitoring of the newborn is recommended, particularly if the baby is preterm, jaundiced, or if the mother started taking AEDs late in pregnancy or after delivery.[135,156]

Prescribing notes — Epilepsy and Breastfeeding

► All mothers should be encouraged to breastfeed and receive support from their health visitor, midwife + GP.[135]

► Parents should be made aware of signs of toxicity in infants of breastfeeding women taking AEDs.[135]

► The possibility of sedation should be considered in infants of mothers taking high dose AEDs, polytherapy, or regimens including primidone, levetiracetam, gabapentin, lamotrigine and topiramate.[135]

Pregnancy and hypertension

Hypertensive disorders occur in up to 10% of all pregnancies.[157] Although the rate of eclampsia in the UK has fallen (less than one woman in every million giving birth now dies from pre-eclampsia in the UK[158]), hypertension in pregnancy remains one of the leading causes of maternal death in the UK.[157]

Categories of hypertensive disorders in pregnancy

Chronic hypertension
Hypertension that is present at, or prior to the booking visit, or before 20 weeks' gestation. As blood pressure tends to fall during the first and second trimesters, a woman with a high blood pressure before 20 weeks' gestation can be assumed to have pre-existing hypertension.[162]

Gestational hypertension
New hypertension presenting after 20 weeks' gestation without significant proteinuria (more than 300 mg of protein in a 24-hour urine collection or more than 30 mg/mmol in a urinary protein/creatinine sample).[162]

Pre-eclampsia
New hypertension presenting after 20 weeks' gestation with significant proteinuria.[162]
Symptoms of pre-eclampsia include:[162]

- Severe headaches (increasing frequency unrelieved by regular analgesics).
- Visual problems, such as blurred vision, flashing lights, double vision, or floating spots.
- Persistent new epigastric pain or pain in the right upper quadrant.
- Vomiting.
- Breathlessness.
- Sudden swelling of the face, hands, or feet.

What pre-conceptual 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:[157]

- There is an increased risk of congenital abnormalities if ACE inhibitors or angiotensin antagonist are taken during pregnancy.[157]
- There is an increased risk of congenital abnormality and neonatal complications if chlorothiazide is taken during pregnancy.[157]
- Other antihypertensive treatments should be discussed with the woman if she is planning pregnancy.[157]
- Stop ACE inhibitors or angiotensin antagonist if the woman becomes pregnant (preferably within 2 working days of notification of pregnancy) and offer alternatives.[157]

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.[159]

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. These changes are related to multiple physiological / environmental factors, and complicate the diagnosis of hypertensive disorders in pregnancy.[160,161]

What is the antihypertensive of choice in pregnancy?

Labetalol, if not contraindicated, is usually the first-line antihypertensive drug in pregnancy.[157] Alternative treatments are methyldopa or nifedipine.[157]

Doses of antihypertensive drugs in pregnancy

► Labetalol: start with a dose of 100 mg twice a day.[162]
► Methyldopa: start with a dose of 250 mg 2–3 times a day.[162]
► Nifedipine: a modified-release preparation should be used and the same brand prescribed for the duration of treatment to ensure consistent bioavailability. Dosages are as recommended for non-pregnant people, and will depend on the brand used.[162]

What target level of blood pressure is recommended in pregnancy?

NICE recommend that pregnant women with chronic hypertension should aim to keep blood pressure <150/100 mmHg (140/90mmHg if there is evidence of target organ damage, e.g. chronic kidney disease) and that women with gestational hypertension are usually only treated when blood pressure is 150/100 to 159/109mmHg or higher.[157]
However, locally, consultant obstetricians aim for lower BP control and aim to keep BP <140/90mmHg.
Excessive reduction of blood pressure should be avoided as this may affect fetal growth.[162]

What are the risks associated with pre-eclampsia?

Pre-eclampsia is a multi-system disorder. It is associated with significant maternal morbidity and mortality.
It can lead to eclamptic seizures, intracerebral haemorrhage, pulmonary oedema, acute renal failure, liver dysfunction, and coagulation abnormalities.[162,163]
Pre-eclampsia and eclampsia can also lead to maternal death, due to intracranial haemorrhage, cerebral infarction, cerebral oedema, acute respiratory distress syndrome and pulmonary oedema, hepatic rupture, or hepatic failure/necrosis.[162,164]
Fetal / neonatal complications include placental abruption, IUGR, premature delivery, intrauterine fetal death, and neonatal death.[162,163]

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).[165]

What is eclampsia?

Eclampsia is a convulsive condition associated with pre-eclampsia.[157] Eclamptic seizures are relatively rare and occur in less than 1% of women with pre-eclampsia.[166]

What factors increase risk of developing pre-eclampsia?

Women are at high risk of pre-eclampsia if they have:

One or more of any of the following high risk factors:[157,162]

- 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.

Two or more of the following moderate risk factors:[157,162]

- 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.

What is the role 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 75mg of aspirin daily from 12 weeks until the birth of the baby.[157] Women with two or more moderate risk factor for pre-eclampsia should also be advised to take 75mg 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.[167]
The use of aspirin for pre-eclampsia is an unlicensed indication.[162]

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.[6162] No increase in bleeding complications, decrease in fetal urine excretion, or significant effects on the ductus arteriosus have been associated with low-dose aspirin.[6,162]
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.[62]

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).[157]

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.[162]

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.
► 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.

Breastfeeding and hypertension

Are anti-hypertensive drugs compatible with breastfeeding?

In women who still need antihypertensive treatment in the postnatal period, diuretic treatment should be avoided if the woman is breastfeeding or expressing milk.[157]
The following antihypertensives are considered to be safe while breastfeeding: labetalol, atenolol, metoprolol, nifedipine, enalapril, and captopril.[162]
There is less safety information available for angiotensin antagonists, amlodipine and ACE inhibitors other than enalapril and captopril.[157]

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.[157]

Prescribing Notes — Hypertension and Breastfeeding

► Diuretic treatment should be avoided.
► Labetalol, atenolol, metoprolol, nifedipine, enalapril, and captopril are considered to be safe.
► There is less safety information available for angiotensin antagonists, amlodipine and ACE inhibitors other than enalapril and captopril.
►The infant should be assessed for adequacy of feeding, at least daily for the first two days after birth.

Pregnancy and hypothyroidism

The prevalence of overt hypothyroidism in pregnancy is 0.2 to 0.5%, with subclinical hypothyroidism in pregnancy between to 2 to 2.5%.[168,169]

What pre-conceptual care is recommended?

Thyroid-stimulating hormone (TSH) and free thyroxine (FT4) levels should be checked before conception if possible, to check adequacy of treatment.[168]
If thyroid function tests (TFTs) are not within the euthyroid range, the woman should be advised to delay conception until she is stabilised on levothyroxine (LT4) treatment.[168]
Women receiving treatment for hypothyroidism should be advised to contact their GP as soon as she thinks she may be pregnant.[168] 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 TSH seen in the first and second trimesters.[170,171] 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 manufactured form of the thyroid hormone, thyroxine (T4). It is considered compatible with all stages of pregnancy.[172] It is essential that pregnant women with hypothyroidism receive adequate levothyroxine replacement therapy.[173] 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.[168]
The dose of levothyroxine should be increased usually by at least 25 to 50 micrograms levothyroxine.[168] 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. In practical terms, the levothyroxine dosage can be doubled on Saturdays and Sundays until early review by a specialist.[174] 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.[168]

Do biochemical reference ranges change during pregnancy?

Yes, the biochemical reference ranges change during pregnancy. TSH is lower throughout pregnancy compared with non-pregnant women.[176] Ideally, during pregnancy, thyroid function tests should be measured using trimester-specific reference ranges. In the absence of this, the recommendation is that, during pregnancy, thyroid function tests are regulated such that serum TSH is kept in the lower half of the normal range (<2.5).[180,189]

How often should thyroid function be monitored in pregnancy?

Check TFTs immediately once pregnancy is confirmed.[168]
If thyroid function is normal when first tested, it seems reasonable to test thyroid function once per trimester.[173,178] If dose adjustment is needed, then 6-weekly tests are probably reasonable.[173]
More frequent tests may be appropriate on specialist advice.

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).[173]

Risks of untreated hypothyroidism?

During the first trimester of pregnancy, maternal T4 is responsible for normal foetal neurological development until the foetal thyroid gland becomes active (which is why there is an increased need of maternal thyroxine in pregnant women).[179]
Untreated or undertreated hypothyroidism has been associated with low birth weight secondary to medically indicated preterm delivery, pre-eclampsia, placental abruption and impaired neuropsychological development of the offspring.[172]

Prescribing Notes: Hypothyroidism and Pregnancy

► 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.
► Certain drugs, especially iron, disturb the absorption of levothyroxine; these medications should be taken at different times.[102]

Pregnancy and hyperthyroidism

The prevalence of hyperthyroidism in pregnancy is 0.1 to 0.4%, with Graves' disease accounting for 85% of these cases.[180,181]

What pre-conceptual 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.[181]
Propylthiouracil is the drug of choice in the first trimester and so should be used pre-conception also.[102]
Women who have recently received radioiodine treatment should be advised to avoid becoming pregnant for at least 6 months after treatment.[181]

Does pregnancy affect hyperthyroidism?

Hyperthyroidism tends to improve in the later stages of pregnancy, necessitating a reduction in dosage. The anti-

thyroid drug can usually be stopped at the beginning of the third trimester. Such spontaneous remission lasts into the postpartum period, but relapse is common three to six months after delivery and should be anticipated, with arrangements for regular TFTs at this time.[182]

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.[185,186] 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.[187]

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.[185]

What management is required?

Management of hyperthyroidism should be carried out exclusively in secondary care, with both a consultant endocrinologist and a consultant obstetrician (important that GPs refer to both).
However, it is helpful if primary care can check serum free thyroxine (FT4), free triiodothyronine (FT3), and TSH levels when pregnancy is confirmed, and send the results to the specialist with the referral.[181] Biochemical monitoring is important to reduce the risk of fetal goitre.[188]

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 as carbimazole has been associated with an increased risk of congenital abnormalities — carbimazole has (very rarely) been associated with neonatal aplasia cutis (a malformation of the scalp).[181,183]
However a switch to carbimazole may be considered in the second trimester due to risk of hepatotoxicity with propylthiouracil.[102]
Both propylthiouracil and carbimazole cross the placenta and can cause fetal goitre and hypothyroidism, so the lowest effective dose should be used.[102]
Radioisotopes should be avoided in pregnancy.[181,183]

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.[183,184]

What is gestational thyrotoxicosis?

Some women, especially those with severe morning sickness, may develop a short term hyperthyroidism (gestational thyrotoxicosis) in the early weeks of pregnancy but this settles without the need for antithyroid drug therapy.[188]
This can occur in women with no previous history of hyperthyroidism, where the patient is not clinically hyperthyroid but biochemically appears so. These ladies don't need any treatment, but to seek expert advice if unsure (to avoid any unnecessary medication).

Prescribing Notes: Hyperthyroidism and Pregnancy

► 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.
► Block-replace regimens are unsuitable.

Breastfeeding and thyroid disorders

Is breastfeeding compatible with drugs used in thyroid disorders?

Drugs used in hypothyroidism

Milk levels of thyroid hormones have not been measured after exogenous administration in humans.[14] However, endogenous liothyronine appears to transfer into milk in higher concentrations than levothyroxine.[14]
As supplementation aims to bring the mother to a euthyroid state, administration of exogenous thyroid hormones should pose no greater risk to the infant than in a normal euthyroid mother.[14]
No adverse effects have been reported in breastfed infants who were exposed to levothyroxine.[14] Thyroxine is a normal component of breast-milk.[14]

Drugs used in hyperthyroidism

There is significant published evidence on the safety of carbimazole and its active metabolite, methimazole in breastfeeding.[14] No adverse effects have been reported in infants at doses of 30mg daily.[14]
There is limited published evidence on the safety of propylthiouracil in breastfeeding.[14] Small amounts are seen in breast milk but no adverse effects have been reported in infants at doses of 300mg daily.[14]
Monitoring the infant's thyroid function should be considered for carbimazole or propylthiouracil, especially in newborn infants, although no cases of thyroid function alteration have been reported.[14]
It is advisable to avoid the iodine/potassium iodide solution used for thyrotoxicosis due to the significant risk of hypothyroidism in the infant.[14]

Prescribing Notes — Thyroid disorders and Breastfeeding

Hypothyroidism
► Levothyroxine is safe and should be continued.

Hyperthyroidism
► Carbimazole or propylthiouracil have limited excretion in breast-milk and so may be used in breast-feeding.
► Use the lowest effective doses of carbimazole or propylthiouracil.
► There is a theoretical risk of infant thyroid suppression with carbimazole at doses >30mg/day and propylthiouracil >300 mg.
► Radioactive iodine is contraindicated.

Patient information

Patient information on Pregnancy and Fertility in Thyroid Disorders is available on the British Thyroid Foundation website: http://www.btf-thyroid.org/information/leaflets/38-pregnancy-and-fertility-guide

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Please note that every effort has been made to ensure that the content of the COMPASS Therapeutic Notes is accurate at the time of publication. Readers are reminded that it is their responsibility to keep up-to-date with any changes in practice.

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COMPASS THERAPEUTIC NOTES ASSESSMENT

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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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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	Asthma attacks are most likely to occur in the first trimester.	T	F
	c	Leukotriene receptor antagonists should not be withheld during pregnancy if clinically indicated.	T	F
	d	Salmeterol is considered to be safe for use in pregnancy.	T	F
2	**In the management of depression in pregnancy**			
	a	Psychological therapy is a useful first line strategy for mild depression.	T	F
	b	Paroxetine is the SSRI of choice in pregnancy.	T	F
	c	SSRI dose should always be tapered close to term.	T	F
	d	Newborns should be monitored for PPHN and poor neonatal adaptation syndrome.	T	F
3	**In the management of diabetes in pregnancy**			
	a	Women with diabetes who are planning to become pregnant should be advised to take folic acid at a dose of 400 micrograms per day.	T	F
	b	Of the women who have diabetes during pregnancy (type 1, type 2 or gestational), the majority will have gestational diabetes.	T	F
	c	Metformin should be discontinued for the duration of the pregnancy.	T	F
	d	Women with gestational diabetes who are on a multiple daily insulin injection regimen 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	Withdrawal of anti-epileptic medication should be the first-line priority in all pregnant women with epilepsy.	T	F
	b	Rates of major congenital malformations are consistently higher with levetiracetam than with other AEDs.	T	F
	c	Children exposed in utero to valproate are at a high risk of serious developmental disorders and/or congenital malformations.	T	F
	d	The children born to mothers taking enzyme-inducing AEDs should be given 1mg 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	Gestational hypertension usually presents in the first trimester.	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