safe practical clinical answers - *fast*

Scenario: Pre-conception advice for all women

What advice should I give a woman planning pregnancy regarding folic acid?

- Assess the risk of a neural tube defect (NTD) for a couple planning a pregnancy.

  - Couples are at high risk of conceiving a child with an NTD if:

  - Either partner has an NTD, or they have had a previous pregnancy affected by an NTD.

  - The woman is taking antiepileptic drugs or has coeliac disease, diabetes, or thalassaemia.

  - All other people have a normal risk of conceiving a child with an NTD.

- Recommend women at high risk of an NTD to take folic acid 5 mg daily and, once pregnant, to continue this until the twelfth week of pregnancy.

- Recommend women who are at normal risk for an NTD to take folic acid 400 micrograms daily, and to continue this until the twelfth week of pregnancy.

- Recommend women with sickle-cell anaemia, to continue taking their normal dose of folic acid 5 mg daily (or to increase the dose to 5 mg), and to continue this throughout pregnancy.

In depth

What advice can I give a woman planning pregnancy about how long it is likely to take to become pregnant?

- Advise women planning pregnancy that for every 100 couples having sexual intercourse 2 to 3 times a week:

  - Around 30 will conceive within 1 month.

  - Around 60 will conceive within 6 months.

  - Around 85 will conceive within 1 year.

  - The remainder will take longer and some of these may need help for them to conceive.

- Advise women planning pregnancy who have been using the progestogen-only injection for contraception that normal fertility may be delayed for up to 1 year after the last injection. Other methods of contraception are not known to have any effect on fertility once they have been discontinued.

In depth

What advice should I give to a woman planning pregnancy who smokes?

- Advise all women planning pregnancy who smoke to stop smoking:

  - Offer women who wish to stop smoking referral to a smoking-cessation service.

  - Advise women who may become pregnant to initially try to stop smoking without using nicotine replacement therapy (NRT).

  - Offer NRT to women who are planning pregnancy, and who have tried and failed to stop smoking without using NRT.

In depth

What advice should I give to a women planning pregnancy, regarding alcohol consumption?

- Advise women planning pregnancy (or who are at any stage of pregnancy) to avoid drinking alcohol. If women do choose to drink, to minimize the risk to the baby, they should not drink more than one to two units of alcohol once or twice a week and should not get drunk.

- Offer support to women who wish to reduce their drinking to within recommended levels but feel unable to do so alone.

  - Provide advice and support in primary care.

  - Offer specialist referral if a women is unable to reduce her drinking with support in primary care.

In depth

What advice should I give to a woman planning pregnancy, who uses illicit drugs?

- Advise women planning pregnancy who use illicit drugs to stop using drugs, if they are able to do so.

- Offer people injecting illicit drugs testing for hepatitis C, hepatitis B, and HIV and refer if tests are positive.

- Offer referral to women planning pregnancy who use illicit drugs and are unable to stop using drugs without support.

- Offer contraceptive advice to women using illicit drugs who may become pregnant before illicit drug use has stopped.

In depth

What advice should I give to women who are planning pregnancy who may be exposed to hazardous substances or radiation?

- Advise women planning pregnancy to read product warning labels before using chemicals.

▪ Advise a woman who is planning pregnancy and is concerned about work exposure to hazardous substances, infections, or radiation, to disclose her intention of becoming pregnant to her employer, if possible.

▪ Advise a woman planning pregnancy, who does not wish to disclose her intention to become pregnant to her employer, that information about the risk of exposure to specific substances can be obtained by telephoning a health and safety expert at the Health and Safety Executive.

In depth

What advice should I give to women planning pregnancy regarding vitamin A, and over-the-counter or herbal medicines?

▪ Advise women planning pregnancy not to take any over-the-counter medicines without consulting a pharmacist to ensure that these products are safe to take if she were to become pregnant.

▪ Advise women planning pregnancy not to take any herbal remedies.

▪ Advise women planning pregnancy not to exceed 10,000 IU of vitamin A (from supplementation), either before becoming pregnant or at any time during pregnancy.

In depth

What advice should I give women planning pregnancy who are overweight or obese?

▪ Advise women who are overweight or obese to lose weight before becoming pregnant.

o Overweight is defined as a BMI between 25 kg/m^2 and 29.9 kg/m^2.

o Obesity is defined as a BMI of 30 kg/m^2 or more.

▪ Target weight for a person who is overweight or obese:

o Women should be informed of the increased health risks their weight poses to themselves and would pose to their unborn child.

o Women should be informed that losing 5–10% of their weight (a realistic target) would have significant health benefits and could increase their chances of becoming pregnant.

o Women should be encouraged to check their weight and waist measurement periodically, or as an alternative, check the fit of their clothes.

▪ Women should be aware that if they do fall pregnant, there is no need to 'eat for two' or to drink full-fat milk.

In depth

What advice should I give a women who wishes to become pregnant regarding cervical screening?

▪ Advise all women planning pregnancy to have a cervical smear test if they are due a test or will be due a test in the near future when they may be pregnant.

In depth

What advice should I give women planning pregnancy regarding immunizations?

▪ Test women planning pregnancy for immunity to rubella if they do not have documented immunity, and vaccinate if the test is negative.

▪ Test women planning pregnancy for immunity to varicella if they do not have a definite history of chickenpox or shingles, and vaccinate if the test is negative and they are eligible for the vaccine. Women are eligible for varicella vaccine include healthcare workers who may come into direct contact with infected patients and healthy, susceptible close contacts of immunocompromised patients.

▪ Vaccinate women planning pregnancy against hepatitis B if they are at high risk of contracting the disease. People at risk include intravenous drug users, those who change sexual partners frequently, those with chronic renal or liver disease, and those who are in close contact with people with hepatitis B.

In depth

How do I manage a woman with previous miscarriage(s)?

▪ Reassure the woman that she still has a good chance of a subsequent successful pregnancy.

▪ Refer women who have had three or more consecutive miscarriages to a gynaecologist for identification and management of any treatable cause.

In depth

Prescriptions

Folic acid - low risk of NTD

Age from 16 to 45 years

Folic acid tablets: 400micrograms once a day

Folic acid 400microgram tablets
Take one tablet once a day.
Supply 90 tablets.

Age: from 16 years to 45 years
NHS cost: £2.24
OTC cost: £3.95
Licensed use: yes

Folic acid - high risk of NTD

Age from 16 to 45 years

Folic acid tablets: 5mg once a day

Folic acid 5mg tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 16 years to 45 years
NHS cost: £4.29
Licensed use: yes

Rubella vaccination (NOT if pregnant)

Age from 16 to 45 years

Rubella vaccine (as MMR) - NOT if pregnant

Measles, Mumps and Rubella live vaccine powder and solvent for solution for injection 0.5ml vials
Give 0.5ml by deep subcutaneous or intramuscular injection. Read attached information.
Supply 1 0.5ml injection.

Age: from 16 years to 45 years
NHS cost: £2.53
Licensed use: yes

Patient information: Do not give vaccine if the woman is/may be pregnant. The woman should avoid getting pregnant for 1 month after the vaccine is given.

Varicella vaccination (NOT if pregnant)

Age from 16 to 45 years

Varicella vaccine (Varilix) - NOT if pregnant

Varicella vaccine (live) powder and solvent for solution for injection 0.5ml vials
Give 0.5ml by subcutaneous injection. Give 2 doses 6 to 8 weeks apart.
Supply 2 0.5ml vials.

Age: from 16 years to 45 years
NHS cost: £54.62
Licensed use: yes
Black triangle

Patient information: Do not give vaccine if the woman is/may be pregnant. The woman should avoid getting pregnant for 6 weeks after the second dose of vaccine is given.

Varicella vaccine (Varivax) - NOT if pregnant

Varicella vaccine (live) powder and solvent for suspension for injection 0.5ml vials
Give 0.5ml by subcutaneous injection. Give 2 doses 4 to 8 weeks apart.
Supply 2 0.5ml vials.

Age: from 16 years to 45 years
NHS cost: £64.28
Licensed use: yes
Black triangle

Patient information: Do not give vaccine if the woman is/may be pregnant. The woman should avoid getting pregnant for 6 weeks after the second dose of vaccine is given.

Hepatitis B vaccination

Age from 16 to 45 years

Hepatitis B vaccine (Engerix B)

Engerix B 20micrograms/1ml suspension for injection pre-filled syringes
Give 1 ml by intramuscular injection. Give a second dose one month later, then give a third dose 6 months after the first dose.
Supply 1 1ml prefilled syringe.

Age: from 16 years to 45 years
NHS cost: £12.99
Licensed use: yes

Hepatitis B vaccine (HBvaxPRO)

HBvaxPRO 10micrograms/1ml suspension for injection vials
Give 1 ml by intramuscular injection. Give a second dose one month later, then give a third dose 6 months after the first dose.
Supply 1 1 ml vial.

Age: from 16 years to 45 years
NHS cost: £12.00
Licensed use: yes

Scenario: Pre-conception advice - women with mental health issues

How do I manage a woman with depression who wishes to become pregnant?

- Refer women with severe depression to a psychiatrist.
- In women with mild or moderate depression assess:

o The safety during pregnancy of the current antidepressant medication, and the possibility of switching to an antidepressant more appropriate for use during pregnancy.

o The risks of stopping any current antidepressant medication in relation to the woman's current mental state, her previous history of depression, and duration of current antidepressant medication.

o Seek specialist advice if unsure whether to try withdrawing or switching an antidepressant.

- Advise the woman not to stop taking her medication unless otherwise directed by the psychiatrist or, in the case of mild or moderate depression, by the primary care practitioner.
- Discuss the standard pre-conception measures (see What to check in all women).

In depth

How do I manage a woman with bipolar disorder who wishes to become pregnant?

- Refer all women with bipolar disorder who wish to become pregnant to a psychiatrist for assessment of bipolar disorder and review of current medication.
- Advise the woman to continue using effective contraception until she has been fully reviewed by the psychiatrist.
- Advise the woman not to stop taking her medication unless otherwise directed by the psychiatrist.
- Discuss the standard pre-conception measures (see What to check in all women).

o Women taking antiepileptic drugs for treatment of their bipolar disorder are considered to be at high risk of conceiving a child with a neural tube defect, and should be prescribed folic acid 5 mg daily.

In depth

How do I manage a woman with schizophrenia who wishes to become pregnant?

- Refer all women with schizophrenia who wish to become pregnant to a psychiatrist for assessment of schizophrenia and review of current medication.
- Advise the woman to continue using effective contraception until a full assessment by the psychiatrist has taken place.

- Advise the woman not to stop taking her medication unless otherwise directed by the psychiatrist.
- Discuss the standard pre-conception measures (see What to check in all women).

Scenario: Pre-conception advice - women with metabolic disorders

How do I manage a woman with thyroid disease who wishes to become pregnant?

- Subclinical hypothyroidism:

o Perform thyroid function tests (TFTs) before conception if they have not been done in the past 6 months.

o If the woman is not receiving levothyroxine treatment, start this whilst waiting for specialist referral.

o Advise women who are planning a pregnancy to consult their GP as soon as they think they may be pregnant as dosage adjustment will be needed.

- Hypothyroidism:

o Ensure optimum control before pregnancy and refer as appropriate.

o Perform TFTs before conception to check adequacy of treatment and to make sure the woman is stable. Ensure she understands the importance of compliance with levothyroxine therapy.

o Advise women who are planning a pregnancy to consult their GP as soon as they think they may be pregnant as dosage adjustment will be needed.

- Hyperthyroidism:

o Refer women who are not already under consultant care, or inform the specialist responsible for the woman's care that she wishes to conceive.

o Advise the woman that frequent monitoring of thyroid function during pregnancy will be required.

o Deferring pregnancy until the course of treatment has been completed may be a better option, if practical.

o For women planning pregnancy within the next 2–3 years, initial treatment with radioactive iodine or surgery may be best.

- Discuss the standard pre-conception measures (see What to check in all women).

In depth

How do I manage a woman with diabetes who wishes to become pregnant?

- Refer all women with diabetes who wish to become pregnant to a pre-conception diabetes clinic (if available) or to their diabetes care team, as soon as possible.

o Advise women with type 2 diabetes that their current medication for diabetes will need to be reviewed, and that they will probably be advised to switch to insulin therapy for the duration of their pregnancy.

- Discuss the importance of optimal blood glucose control with the woman.

- Women planning pregnancy should aim to achieve a pre-conception glycosylated haemoglobin (HbA_{1c}) value of < 7%.
- Advise the woman to continue using effective contraception methods until this target has been achieved.

- Ensure that complications of diabetes are reviewed.
- Ensure that concurrent medication is reviewed.
- Measure thyroid stimulating hormone, free thyroxine, and thyroid peroxidase antibodies in women with type 1 diabetes.
- Discuss the standard pre-conception measures (see What to check in all women).

- Women with diabetes are considered to be at high risk of conceiving a child with a neural tube defect and should be prescribed folic acid 5 mg daily.

Scenario: Pre-conception advice - women with chronic medical conditions

What general issues should I discuss with a woman with a chronic medical condition who wishes to become pregnant?

- Discuss the importance of continuing to use effective contraception until a full assessment of the woman's condition and her current medication has taken place.
- Advise the woman not to stop taking her current medication unless otherwise directed by a clinician.
- Discuss the standard pre-conception measures (see What to check in all women).

How do I manage a woman with epilepsy who wishes to become pregnant?

- Reassure the woman that, even on antiepileptic medication, there is a 90% chance of having a normal pregnancy and delivery.
- Refer all women taking antiepileptic drugs (AEDs) to a specialist for review of epilepsy treatment *before* the woman becomes pregnant, to discuss the relative risks and benefits of adjusting her medication.
- Women taking AEDs are considered to be at high risk of conceiving a child with a neural tube defect and should be prescribed folic acid 5 mg daily.

In depth

How do I manage a woman with chronic cardiac disease who wishes to become pregnant?

- Refer all women with cardiac disease who wish to become pregnant to a cardiologist for accurate diagnosis and functional assessment so that maternal and fetal risk can be assessed.

In depth

How do I manage a woman with chronic hypertension who wishes to become pregnant?

▪ Refer all women with a history of hypertension who wish to become pregnant to a cardiac specialist prior to becoming pregnant.

▪ Advise the woman that she will be at increased risk of pre-eclampsia during pregnancy, and that she will require careful monitoring.

In depth

How do I manage a woman with renal disease who wishes to become pregnant?

▪ Refer women who have renal disease and are planning a pregnancy to a specialist for assessment.

In depth

How do I manage a woman with venous thromboembolism who wishes to become pregnant?

▪ Screen all women with a personal or immediate family history of venous thromboembolism (VTE) for both inherited and acquired thrombophilia. Thromboprophylaxis, either in the first trimester or post-partum, may be required.

▪ Seek specialist advice for women who have a past history of deep vein thrombosis or pulmonary embolism, and for those with an abnormal thrombophilia screen.

▪ Refer all women receiving warfarin therapy who are planning a pregnancy to a specialist for advice, as warfarin will need to be stopped or replaced by heparin, depending on the woman's degree of risk of VTE.

In depth

How do I manage a woman with asthma who wishes to become pregnant?

▪ In women with mild-to-moderate asthma, ensure that asthma is well controlled.

▪ For women with severe asthma and those in whom asthma is poorly controlled, refer to a chest physician to ensure adequate control and monitoring.

▪ Discuss the importance of continuing to take asthma medication as prescribed, both before conception and throughout the pregnancy, to maintain good asthma control.

In depth

How do I manage a woman with rheumatoid arthritis who wishes to become pregnant?

▪ Refer all women with rheumatoid arthritis who wish to become pregnant to a rheumatologist, especially if they are taking nonsteroidal anti-inflammatory drugs (NSAIDs) or disease-modifying anti-rheumatic drugs (DMARDs).

▪ Ensure the use of effective contraception whilst taking DMARDs. Because of their long half life, some DMARDs may need to be discontinued several months before a planned conception.

Scenario: Pre-conception advice - women with genetic haemoglobinopathies

How do I manage a woman with thalassaemia who wishes to become pregnant?

- **Refer all women with thalassaemia** to a haematologist for assessment.
- **Women who are carriers:**

o Seek advice from a haematologist or haemoglobinopathy counsellor (if available) for women who are carriers and have an unusual variant or need further investigation.

o Ensure that the woman's partner has been tested.

- Discuss the standard pre-conception measures (see What to check in all women).

o Women with thalassaemia and women who are carriers should receive folic acid 5 mg daily throughout the pregnancy.

In depth

How do I manage a woman with sickle-cell disease who wishes to become pregnant?

- **Refer all women with a sickle-cell disease to a haematologist** for assessment and monitoring.
- Advise the woman to continue using adequate contraception until she has been fully assessed by a haematologist.
- Women who are carriers should be treated as for a normal pregnancy.
- Discuss the standard pre-conception measures (see What to check in all women).

o Ensure women with HbS/S or HbS/C disease are taking folic acid 5 mg for life.

o Women who are carriers should receive folic acid 400 micrograms daily.

Scenario: Advice for older women regarding their risk of having a Down's syndrome baby

What advice can I give older women who are planning a pregnancy about their risks of having a baby with a chromosomal abnormality such as Down's syndrome?

- Discuss the standard pre-conception measures (see What to check in all women).
- **Advise women planning pregnancy who are concerned about the risks of chromosomal abnormalities, such as Down's syndrome, that the risk increases with maternal age** and after a previously-affected pregnancy. The risk of Down's syndrome is given in Table 1 below:

Table 1. Risk of Down's syndrome with increasing maternal age.

Age of mother	Risk
20 years	1:1500
30 years	1:800
35 years	1:270
40 years	1:100
45 years and over	1:50 and greater

- Advise that there is no pre-conception test that can predict whether a couple will conceive a baby with a chromosomal abnormality such as Down's syndrome.
- Advise that antenatal screening tests can estimate the likelihood of a pregnant woman carrying a baby with Down's syndrome.
- Advise that a definitive diagnostic test for Down's syndrome is offered to pregnant women at high risk. This can be established by amniocentesis, chorionic villus sampling, or fetal blood sampling. It is important that they are aware that testing carries a risk of fetal death but this occurs in less than 1% of cases.

Scenario: Advice regarding when to refer for genetic screening

What pre-conception advice can I give to a couple who are at a higher risk of having a baby with an inherited genetic disorder including haemoglobinopathies?

- Discuss the standard pre-conception measures (see What to check in all women).
- **Offer haemoglobinopathy screening to all women planning a pregnancy** by sending blood samples for testing and asking them to complete a family of origin questionnaire, available at www.sickleandthal.org.uk (pdf):

O Take blood for full blood count and electrophoresis:

O From all women from high prevalence areas.

O From all women from low prevalence areas if they or their partner come from a population (identified by the questionnaire) at increased risk of a haemoglobinopathies.

O Take blood for full blood count alone:

O From women from low prevalence areas who come from a population (identified by the questionnaire) at low risk of haemoglobinopathies.

O Screen men for haemoglobinopathies only if the women is identified as a carrier.

- **Offer referral for genetic screening and counselling to couples that are planning pregnancy who:**

O Have a personal or family history of an inherited genetic disorder.

O Have had a previous pregnancy affected by an inherited genetic disorder.

- Are Ashkenazi Jews (for Tay–Sachs disease).

▪ **Offer referral for pre-natal diagnosis testing** to women who would consider termination of an effected pregnancy when they are known to be a carrier of a recessively inherited genetic disorder and:

- The father of the baby is known to be a carrier for the same disorder or,
- The carrier status of the father is unknown and cannot be established.

▪ **Advise women who would consider termination of an affected pregnancy** that it is important that they present early in pregnancy, ideally, if they want to avoid a termination after the first trimester.

▪ **The most common genetic disorders requiring referral** for genetic screening are included in Table 1.

Table 1. Most common genetic disorders requiring referral for testing.

Genetic disorder	Condition
Dominantly-inherited disorders	Neurofibromatosis
	Tuberous sclerosis
	Huntington's disease
	Adult polycystic disease
	Marfan's syndrome
	Achondroplasia
Recessively-inherited disorders	Haemoglobinopathies
	Cystic fibrosis
	Tay–Sachs disease
	Gaucher's disease
	Congenital adrenal hyperplasia
	Friedrich's ataxia
	Spinal muscular atrophy
X-linked disorders	Duchenne's muscular dystrophy
	Fragile X syndrome
	Haemophilias A and B
	Glucose-6-phosphate dehydrogenase deficiency

[Farndon and Kilby, 1999]

In depth

CKS safe practical clinical answers - *fast*

What do I need to assess in a woman planning pregnancy?

Each part of the assessment identifies a specific management requirement. Further information about how to assess and manage individual components is provided by following the hyperlinks.

Assess the following in a woman who is planning to become pregnant:

- When is she planning pregnancy?
- Is she currently taking folic acid and if so, is she taking an appropriate dose for her risk of a neural tube defect?
- Is she up to date with her cervical smear?
- Is she a smoker?
- How many units of alcohol does she drink each week?
- Does she use illicit drugs?
- Does she have immunity to rubella?
- Does she have a definite history of chickenpox or shingles?
- Is she at high risk of hepatitis B?
- Does she have any concerns about work exposure to hazardous substances or radiation?
- Is she taking over-the-counter medicines, vitamins, or herbal remedies?
- Is she overweight?
- Does she have a chronic health problem? Pre-conception management advice is provided for:

o Depression

o Bipolar disorder

o Schizophrenia

o Epilepsy

o Diabetes

o Thyroid disease

o Chronic hypertension

o Chronic cardiac disease

- Renal disease
- Asthma
- Thalassaemia
- Sickle-cell disease
- Previous thromboembolism
- Rheumatoid arthritis

▪ Has she had a previous miscarriage?

▪ Has she or her partner expressed concerns about their risk of having a baby with a chromosomal abnormality such as Down's syndrome?

▪ Is she or her partner at increased risk of having a baby with an inherited genetic disorder?

What should I check in all women planning pregnancy?

What advice can I give a woman planning pregnancy about how long it is likely to take to become pregnant?

▪ **Advise women planning pregnancy that for every 100 couples having sexual intercourse 2 to 3 times a week:**

- Around 30 will conceive within 1 month.
- Around 60 will conceive within 6 months.
- Around 85 will conceive within 1 year.
- The remainder will take longer and some of these may need help for them to conceive.

▪ **Advise women planning pregnancy who have been using the progestogen-only injection for contraception** that normal fertility may be delayed for up to 1 year after the last injection. Other methods of contraception are not known to have any effect on fertility once they have been discontinued.

Clarification / Additional information

▪ For further information about what to do if a couple is having difficulty conceiving see the CKS topic on Infertility.

Basis for recommendation

▪ **The statistics about the time taken for 100 couples to conceive** are derived from statistics quoted in authoritative literature, including the Oxford Textbook of Medicine [Jacobs, 2003].

▪ **The advice about the delay to normal fertility with injected progestogen only contraception** is derived from evidence reported by the National Institute for Health and Clinical Excellence [NICE, 2005].

What advice should I give a woman planning pregnancy regarding folic acid?

▪ **Assess the risk of a neural tube defect (NTD) for a couple planning a pregnancy.**

o **Couples are at high risk of conceiving a child with an NTD if:**

o Either partner has an NTD, or they have had a previous pregnancy affected by an NTD.

o The woman is taking antiepileptic drugs or has coeliac disease, diabetes, or thalassaemia.

o **All other people have a normal risk of conceiving a child with an NTD.**

▪ **Recommend women at high risk of an NTD** to take folic acid 5 mg daily and, once pregnant, to continue this until the twelfth week of pregnancy.

▪ **Recommend women who are at normal risk for an NTD** to take folic acid 400 micrograms daily, and to continue this until the twelfth week of pregnancy.

▪ **Recommend women with sickle-cell anaemia,** to continue taking their normal dose of folic acid 5 mg daily (or to increase the dose to 5 mg), and to continue this throughout pregnancy.

Basis for recommendation

Basis for recommending folic acid supplements to all women:

▪ There is compelling evidence in a Cochrane systematic review that examined the effect of folic acid on the incidence of neural tube defects (NTDs). It concluded that 'periconceptual folate supplementation has a strong protective effect against neural tube defects' [Lumley et al, 2001].

o **Population included in the study:** 6425 women with and without pregnancies previously affected by an NTD.

o **Intervention:** periconceptual folate supplementation in doses ranging from 0.36–4.0 mg daily.

o **Comparison:** placebo.

o **Outcomes — benefits:** periconceptual folate supplementation reduced the incidence of NTD (RR 0.28, 95% CI 0.13 to 0.58).

o **Outcomes — harms:** no significant harms were detected from folic acid supplementation, and it did not significantly increase the risk of miscarriage, ectopic pregnancy, or stillbirth.

Basis for recommending high dose folate supplementation to women at high risk of an NTD:

▪ The recommendation to prescribe folic acid 5 mg to people at higher risk of an NTD and 400 micrograms to people at normal risk of NTD is based on the recommendations of an expert advisory group in 1992, and

reiterated by the National Institute for Health and Clinical Excellence in their antenatal care guideline in 2003 [Expert Advisory Group et al, 1992, National Collaborating Centre for Women's and Children's Health, 2003]. A woman is considered to be at high risk of conceiving a child with an NTD if:

o Either she or her partner (or a first-degree relative) have had a previous pregnancy affected by an NTD, or if either suffers from the condition themselves (the risk is increased about ten-fold) [MRC Vitamin Study Research Group, 1991; Expert Advisory Group et al, 1992].

o She has coeliac disease (when dietary intake of folate is likely to be compromised due to inability to digest wheat products) [DH, 2000; BNF 47, 2004].

o She has type 1 or type 2 diabetes [CEMACH, 2006].

o She is taking an anti-epileptic medication [BNF 47, 2004].

o She has thalassaemia or she is a thalassaemia carrier. Although inconclusive, data suggest that there is a higher prevalence of NTD among women who are thalassaemia carriers:

o In one study, women were referred to a tertiary centre for prenatal diagnosis [Lam and Tang, 1999]. Of the 1961 women referred, 206 women were alpha-thalassaemia heterozygotes and 102 women were beta-thalassaemia heterozygotes. Three alpha-thalassaemia carriers and one beta-thalassaemia carrier had a pregnancy affected by anencephaly compared with five of the 1523 non-carrier pregnancies available for follow-up, which were affected by spina bifida (OR 3.99, 95% CI 1.07 to 14.94; $p < 0.05$).

o A second study (n = 75 women with a pregnancy affected by an NTD) found that the prevalence of thalassaemia carriers who had a pregnancy affected by an NTD was significantly higher than in the general population (22.5% versus 14%; $p < 0.05$) [Ibba et al, 2003].

Basis for recommending high dose folic acid supplements in women with sickle-cell anaemia:

▪ Women with sickle-cell anaemia have an increased requirement for folic acid, due to the increased production of red blood cells, and are advised to take lifelong folic acid supplements. Experts advise that women should continue taking folic acid at a dose of 5 mg daily throughout their pregnancy [Oteng-Ntim et al, 2003; Oteng-Ntim et al, 2006].

What advice should I give to a woman planning pregnancy who smokes?

▪ **Advise all women planning pregnancy who smoke to stop smoking:**

o Offer women who wish to stop smoking referral to a smoking-cessation service.

o Advise women who may become pregnant to initially try to stop smoking without using nicotine replacement therapy (NRT).

o Offer NRT to women who are planning pregnancy, and who have tried and failed to stop smoking without using NRT.

▪ Do not prescribe bupropion or varenicline to women who may become pregnant.

Clarification / Additional information

▪ For further information about how to manage a woman who wishes to stop smoking see the CKS topic on Smoking cessation.

Basis for recommendation

Why advise women who smoke and wish to become pregnant to stop smoking?

▪ Smoking in pregnancy increases the risk of miscarriage, preterm delivery, reduced birthweight, and perinatal death [Dobson et al, 1998].

▪ Women who quit before pregnancy are less likely to relapse [DiClemente et al, 2000; Lumley et al, 2004].

Why offer referral to a smoking-cessation service?

▪ There is evidence from a Cochrane systematic review of the effectiveness of these interventions at reducing the number of women who are pregnant and smoke [Lumley et al, 2004].

Why advise women who may become pregnant to initially try to stop smoking without using NRT?

▪ In the early stages of pregnancy a woman may not be aware that she is pregnant. For women using NRT this exposes the fetus to nicotine. The risk of this exposure to the fetus has not been established, and is avoided if the woman can stop smoking without using NRT.

Why offer NRT to women who have tried and failed to stop smoking without using NRT?

▪ Cigarette smoking, in general, delivers more nicotine than NRT, and also exposes the mother and fetus to many other toxins. NRT is likely to be appreciably safer than continued smoking, and can theoretically be justified in pregnant women in whom non-pharmacological interventions have failed [RCP, 1999; Dempsey and Benowitz, 2001].

Why is bupropion or varenicline not recommended to women who may become pregnant?

▪ There is a lack of data available on the safety of these drugs during pregnancy. If bupropion is prescribed, the course should be completed before the woman tries to become pregnant [NICE, 2002].

What advice should I give to a women planning pregnancy, regarding alcohol consumption?

▪ **Advise women planning pregnancy (or who are at any stage of pregnancy) to avoid drinking alcohol.**

o If women do choose to drink, to minimize the risk to the baby, they should not drink more than one to two units of alcohol once or twice a week and should not get drunk.

▪ **Offer support to women who wish to reduce their drinking** to within recommended levels but feel unable to do so alone.

o Provide advice and support in primary care.

o Offer specialist referral if a women is unable to reduce her drinking with support in primary care.

Clarification / Additional information

▪ **One unit of alcohol:**

o In the UK one unit is defined as a drink containing 8 g of ethanol. This is equivalent to:

o Half a pint of average strength beer, lager, or cider (3–4% alcohol by volume [ABV]).

o Small pub measure (25 mL) of spirits (40% ABV).

o Standard pub measure (50 mL) of fortified wine, for example sherry, port (20% ABV).

o A small glass (125 mL) of average strength wine (12% ABV) contains 1.5 units of alcohol.

o A standard pub measure (35 mL) of spirits (40% ABV) contains 1.5 units of alcohol.

▪ **Specialist referral for people who are unable to reduce their drinking:**

o A fetus is at risk of harm from levels of alcohol consumption that are unlikely to have any long term risks to the heath of the mother. Levels of drinking that are considered harmful to a women's health should not be used as a guide for when to refer a women who may become pregnant.

▪ For further information on how to provide advise and support for a person who wishes to reduce their drinking, see the CKS topic on Alcohol - problem drinking.

Basis for recommendation

▪ The recommendation for women to avoid alcohol if they are pregnant or trying to conceive comes from the Department of Health [DH, 2007]. This updated advice is not a result of new scientific evidence, but is consistent with the current evidence. The advice has been revised to make it easier to understand and to provide consistent advice across the UK.

▪ A statement by the Royal College of Obstetricians and Gynaecologists, following a review of the evidence, concludes that [RCOG, 2006]:

o 'There is an increasing body of evidence suggesting harm to the fetus from alcohol consumption during pregnancy. While the safest approach may be to avoid any alcohol intake during pregnancy, it remains the case

that there is no evidence of harm from low levels of alcohol consumption, defined as no more than one or two units of alcohol once or twice a week'.

o Binge drinking in early pregnancy may be particularly harmful.

▪ Women who are planning pregnancy may become pregnant at any time, and in the early stages of pregnancy may be unaware of that they are pregnant. Therefore, the recommendations for safe drinking levels for pregnant women should also be applied to women planning pregnancy.

What advice should I give to a woman planning pregnancy, who uses illicit drugs?

▪ **Advise women planning pregnancy who use illicit drugs to stop using drugs,** if they are able to do so.

▪ Offer people injecting illicit drugs, testing for hepatitis C, hepatitis B, and HIV and refer if tests are positive.

▪ Offer referral to women planning pregnancy who use illicit drugs and are unable to stop using drugs without support.

▪ Offer contraceptive advice to women using illicit drugs who may become pregnant before illicit drug use has stopped.

Clarification / Additional information

▪ **Offering contraceptive advice to women who may become pregnant before stopping illicit drug use:**

o Women may become pregnant when there is a delay in stopping illicit drug use. This delay may occur because:

o They may not be motivated to stop their drug use.

o Referral to specialist drugs and alcohol services takes time.

o Treatment and withdrawal from illicit drugs may take time to complete.

o For further information see the CKS topic on Contraception.

▪ **Referring women who are using illicit drugs to specialist drugs and alcohol services:**

o Refer women who are unable to stop using illicit drugs without specialist help.

o Women using opioids may be offered stabilization and maintenance on methadone in place of complete withdrawal from opioids.

o For further information about managing pregnant women who are dependant on opioids, see the CKS topic on Opioid dependence.

Basis for recommendation

- **Basis for advice to stop any illicit drug use before conception:**

o The fetus is particularly vulnerable to the harmful effects of drugs. No illicit drugs have definitely been established as safe during pregnancy.

o It is therefore widely recommended by experts that all illicit drugs should be avoided during pregnancy.

- **Evidence from a number of studies have reported an increased risk of fetal harms from cocaine use during pregnancy,** including [Shankaran et al, 2007]:

o Higher rate of premature birth.

o Lower birth weight.

o Smaller head circumference.

o Intracerebral haemorrhage.

o Behavioural problems that persist until at least 7 years old in children born to mothers that were heavy cocaine users during pregnancy.

- **A number of studies have reported harms to the fetus from illicit opioid use during pregnancy.** However, confounding factors, such as high rates of smoking and poor diet in this population, mean that it is difficult to determine the size of the effect directly caused by opioid use. Harms reported include [Shankaran et al, 2007]:

o Low birth weight.

o Intrauterine growth retardation.

o Infant distress due to acute drug withdrawal after delivery.

- **Basis for hepatitis C, hepatitis B, and HIV testing [RCGP, 2007]:**

o Hepatitis C is transmitted to the fetus in up to 6% of people with chronic infection. It is not thought to occur in people who have been infected but have cleared the virus, either naturally or following treatment.

o Treatment with ribavirin and interferon is successful in clearing the virus in between 40 to 60% of people. Treatment prior to conception can prevent fetal infection.

o There are no pre-conception treatments to prevent transmission of HIV or hepatitis B to the fetus but it is sensible to test for these conditions at the same time when there is a clear risk factor.

What advice should I give to women who are planning pregnancy who may be exposed to hazardous substances or radiation?

- **Advise women planning pregnancy to read product warning labels before using chemicals.**

▪ **Advise a woman who is planning pregnancy and is concerned about work exposure to hazardous substances, infections, or radiation, to discuss her intention of becoming pregnant with her employer, if possible.**

▪ **Advise a woman planning pregnancy who does not wish to discuss her intention to become pregnant with her employer,** that information about the risk of exposure to specific substances can be obtained by telephoning a health and safety expert at the Health and Safety Executive.

Clarification / Additional information

▪ Further information is available on the Health and Safety Executive website at www.hse.gov.uk. This includes:

o The health and safety obligations of employees and employers with regards to hazardous substances and radiation.

o Information about the risks of specific substances.

o The telephone number of an expert for discussion of the risks of specific substances.

Basis for recommendation

Basis for recommending a woman discusses her intention to become pregnant with her employer:

▪ **An employer is legally obliged to [UK Parliament, 1999]:**

o Ensure that employees are informed of all potential risks to their health and safety.

o Assess the health and safety risks for different groups of employees, including the risks to women of childbearing age who could be in the early stages of pregnancy but unaware that they are pregnant.

o Inform all women of childbearing age of potential hazards in their workplace.

o Implement all reasonable health and safety measures identified by the assessment as being necessary, to remove or reduce the risk to women of childbearing age.

▪ By discussing her intention to become pregnant with her employer, a woman has the opportunity to discuss any concerns she may have about her exposure to hazardous substances.

▪ Knowing that she intends to become pregnant, her employer may need to take reasonable measures to reduce or remove any potential risks to the woman.

What advice should I give to women planning pregnancy regarding vitamin A, and over-the-counter or herbal medicines?

▪ **Advise women planning pregnancy not to take any over-the-counter medicines,** without consulting a pharmacist to ensure that these products are safe to take if they were to become pregnant.

▪ **Advise women planning pregnancy not to take any herbal remedies.**

▪ **Advise women planning pregnancy not to exceed 10,000 IU of vitamin A (from supplementation),** either before becoming pregnant or at any time during pregnancy.

Clarification / Additional information

▪ Vitamin A can be obtained in two forms, vitamin A (retinol) and pro-vitamin A (beta-carotene).

o Beta-carotene is converted to vitamin A as needed by the body and therefore, there are no concerns over the safety of beta-carotene supplementation.

o The composition of a daily vitamin supplements is now limited to a maximum of 6000 IU of vitamin A. As long as a person does not exceed the recommended daily intake of vitamins they will remain well within the safe daily dose for vitamin A.

[Schaefer et al, 2007]

Basis for recommendation

Basis for recommending that women seek advice from a pharmacist about the safety of over-the-counter medicines:

▪ Some over-the-counter medicines, such as ibuprofen, are not recommended during pregnancy because of their potential to harm the fetus.

▪ Women who are trying to become pregnant may not be aware they are pregnant in the early stages, when the fetus is at its most vulnerable to the harmful effects of certain drugs.

Basis for recommending that women planning pregnancy do not to take any herbal remedies:

▪ Herbal remedies are unlicensed products and there is little or no information on their safety immediately before or during pregnancy.

Basis for recommending limiting vitamin A supplementation in pregnancy:

▪ There is evidence that taking more than 10,000 IU of vitamin A daily from supplementation may result in an increased incidence of birth defects [WHO, 1998].

What advice should I give women planning pregnancy who are overweight or obese?

▪ Advise women who are overweight or obese to lose weight before becoming pregnant.

o Overweight is defined as a BMI between 25 kg/m^2 and 29.9 kg/m^2.

o Obesity is defined as a BMI of 30 kg/m^2 or more.

▪ Target weight for a person who is overweight or obese:

o Women should be informed of the increased health risks their weight poses to themselves and would pose to their unborn child.

o Women should be informed that losing 5–10% of their weight (a realistic target) would have significant health benefits and could increase their chances of becoming pregnant.

o Women should be encouraged to check their weight and waist measurement periodically, or as an alternative, check the fit of their clothes.

▪ Women should be aware that if they do fall pregnant, there is no need to 'eat for two' or to drink full-fat milk.

Clarification / Additional information

Body mass index (BMI):

▪ The body mass index (BMI) is calculated by dividing the body weight in kilograms by the square of the height in metres.

▪ For further information on managing people who are overweight or obese, see the CKS topic on Obesity.

Target weight for a person who is overweight or obese:

▪ People that are overweight or obese are at an increased risk of adverse pregnancy outcomes compared to people who are not overweight. This risk is proportional to a person's BMI with the increased risk being modest in a person who is overweight but significant in people who are obese, particularly people with a BMI of over 40 kg/m^2.

▪ It is impractical to expect most people who are overweight or obese to reduce their weight to their ideal body weight. However, they should be informed of their increased risk of adverse pregnancy outcomes caused by their excess weight and supported in their efforts to reduce weight as much as possible before becoming pregnant.

▪ Weight loss programmes are not recommended during pregnancy as they may harm the health of the unborn child. There are no evidence-based UK guidelines on recommended weight-gain ranges during pregnancy, and there is great variability in the amount of weight pregnant women can gain during pregnancy.

Basis for recommendation

The recommendation to advise women of the potential health risks to themselves and their unborn child, and the target weight loss suggested, are based on the NICE public health guidance *Weight management before, during and after pregnancy* [NICE, 2010].

Health risks of obesity for mother and child

▪ Increasing obesity (higher body mass index [BMI]) is associated with proportionally increased risk of adverse pregnancy outcomes.

▪ Studies that demonstrate that women who are overweight or obese have a greater risk of an adverse pregnancy outcome compared with women who are not overweight. These adverse pregnancy outcomes include **[Cedergren, 2004; Villamor and Cnattingius, 2006]**:

o Pre-eclampsia, odds ratio (OR) 4.82 (95% CI 4.04 to 5.74)

o Antepartum stillbirth, OR 2.79 (95% CI 1.95 to 4.02)

o Caesarean section, OR 2.69 (95% CI 2.49 to 2.90)

o Instrumental delivery, OR 1.34 (95% CI 1.16 to 1.56)

o Shoulder dystocia, OR 3.14 (95% CI 1.86 to 5.31)

o Fetal distress, OR 2.52 (95% CI 2.12 to 2.99)

o Early neonatal death, OR 3.41 (95% CI 2.07 to 5.63)

Dietary advice if a woman falls pregnant

▪ This recommendation is based on the fact that energy needs do not change in the first 6 months of pregnancy, and in the last 3 months of pregnancy they increase slightly by approximately 200 calories per day [NICE, 2010].

What advice should I give a women who wishes to become pregnant regarding cervical screening?

▪ **Advise all women planning pregnancy who are due a cervical smear test to have the test as soon as possible, *before* becoming pregnant.**

Basis for recommendation

▪ Cervical smears are not routinely taken during pregnancy as pregnancy-related inflammatory changes make them difficult to interpret.

What advice should I give women planning pregnancy regarding immunizations?

- **Test women planning pregnancy for immunity to rubella** if they do not have documented immunity, and vaccinate if the test is negative.
- **Test women planning pregnancy for immunity to varicella** if they do not have a definite history of chickenpox or shingles, and vaccinate if the test is negative and they are eligible for the vaccine.
- **Vaccinate women planning pregnancy against hepatitis B** if they are at high risk of contracting hepatitis B.

Clarification / Additional information

Rubella:

- **Women are considered immune to rubella when [DH, 2006c]:**

o A rubella antibody screening test has detected antibodies.

o At least two documented doses of rubella vaccine have been given.

- **Vaccinating against rubella [DH, 2006c]:**

o The measles, mumps, and rubella (MMR) combined vaccine is now used for immunization of unprotected women of childbearing age, due to the non-availability of single rubella vaccine.

o Women should be advised to use effective contraception to avoid becoming pregnant for 1 month after receiving rubella-containing vaccine, although surveillance of women immunized during pregnancy, including 293 immunized during the high-risk period 6 weeks after the last menstrual period, failed to detect any significant problems.

Varicella:

- **Women are eligible for varicella vaccination when they are [DH, 2006a]:**

o Healthcare workers who come into direct contact with patients.

o Healthy, susceptible close contacts of immunocompromised patients.

- **Women are considered immune to varicella when [DH, 2006a]:**

o They have a definite history of chickenpox or *Herpes zoster*.

o They do not have a definite history of chickenpox or *Herpes zoster*, but testing has demonstrated varicella immunity.

Hepatitis B:

- **People are considered at risk of hepatitis B if they [DH, 2006b]:**

o Are intravenous drug users or at risk of starting to inject, such as people that presently smoke heroin or crack cocaine.

o Change partners frequently, particularly commercial sex workers and men who have sex with men.

o Are in close contact with people with acute or chronic hepatitis B or in close contact with people at risk of developing hepatitis B. This includes:

o Health workers.

o Close family contacts of someone with the disease, or at risk of developing the disease.

o People travelling to, or going to reside in, areas of high or intermediate prevalence of the disease.

o People in prison.

o Individuals with learning difficulties in residential accommodation.

o Have chronic renal failure.

o Have chronic liver disease.

Basis for recommendation

Basis for recommending immunization against rubella for non-immune women who are planning pregnancy [DH, 2006c]:

▪ Maternal immunity to rubella prevents infection which can cause fetal death or congenital rubella syndrome. This syndrome is most likely when infection occurs in the first 8–10 weeks of pregnancy and includes:

o Cataracts and other eye defects.

o Deafness.

o Cardiac abnormalities.

o Microcephaly.

o Intrauterine growth retardation.

o Inflammatory lesions of brain, liver, lungs, and bone marrow.

Basis for recommending the restricted use of varicella immunization [DH, 2006a]:

▪ It is recommended that varicella immunization is restricted to healthcare workers who come into direct contact with patients and healthy, susceptible close household contacts of immunocompromised patients because:

o Although there would be benefit from immunizing the general population against varicella, the supply of vaccine is limited. Therefore, the Department of Health recommends restricting its use to those at greatest risk and for whom there is evidence that it is likely to be effective.

Basis for recommending immunization against varicella for non-immune women planning pregnancy who are eligible for the vaccine [DH, 2006a]:

▪ **To prevent fetal harm following maternal varicella infection.** These harms include:

o **In the first 20 weeks of pregnancy,** congenital (fetal) varicella syndrome. This syndrome includes, limb hypoplasia, microcephaly, cataracts, growth retardation, and skin scarring.

o **In the second and third trimesters of pregnancy,** herpes zoster may result in an otherwise healthy infant. Occasional cases of fetal damage comprising chorioretinal damage, microcephaly, and skin scarring may result.

o **In the last 7 days before, to a week after, delivery,** severe and even fatal disease in the neonate.

▪ **To prevent maternal harm in the second and third trimester of pregnancy.** Maternal deaths have been reported due to varicella infections between 27 and 32 weeks gestation.

Basis for recommending immunization against hepatitis B for women planning pregnancy who are at risk of contracting hepatitis B [DH, 2006b]:

▪ Maternal immunization against hepatitis B prevents infection that can be transmitted to the baby perinatally.

How do I manage a woman with previous miscarriage(s)?

▪ **Reassure the woman** that she still has a good chance of a subsequent successful pregnancy.

▪ **Refer women who have had three or more consecutive miscarriages to a gynaecologist** for identification and management of any treatable cause.

Clarification / Additional information

▪ Recurrent miscarriage is defined as the loss of three or more pregnancies. Recurrent miscarriage has many possible causes and a number of factors may underlie the recurrent losses.

[RCOG, 2003]

Basis for recommendation

▪ Miscarriage is relatively common, occurring in 10–15% of all clinically-recognized pregnancies [RCOG, 2003].

o If the last pregnancy ended normally, the risk of miscarriage in the next pregnancy is reduced to about 5%.

o If the last pregnancy ended in miscarriage, the risk of miscarriage in the next pregnancy is increased to about 20% [Regan et al, 1989].

o Around 1% of women have recurrent miscarriages (loss of three or more pregnancies before 23 weeks) [RCOG, 2003] (greater than expected by chance alone).

▪ A woman who has had three consecutive miscarriages still has a 60–75% chance of a successful fourth pregnancy [Drife and Magowan, 2004].

▪ It is recommended that the woman is referred to a gynaecologist for identification and management of any treatable cause [Khot and Polmear, 2003].

o Conditions associated with recurrent miscarriage include [Chamberlain and Morgan, 2002; RCOG, 2003]:

o Antiphospholipid syndrome

o Genetic factors

o Thrombophilia

o Incompetent cervix

o Fibroids

o In a significant proportion (> 50%) of women who have recurrent miscarriages, the cause remains unexplained despite investigation. In these women the prognosis for a successful future pregnancy with supportive care alone is about 25% [RCOG, 2003; Drife and Magowan, 2004].

How do I manage a woman with a chronic health problem?

How do I manage a woman with depression who wishes to become pregnant?

▪ **Refer women with severe depression to a psychiatrist.**

▪ **In women with mild or moderate depression assess:**

o The safety during pregnancy of current antidepressant medication, and the possibility of switching to an antidepressant more appropriate for use during pregnancy.

o The risks of stopping current antidepressant medication in relation to the woman's current mental state, her previous history of depression, and duration of current antidepressant medication.

o Seek specialist advice if unsure whether to try withdrawing or switching antidepressant.

▪ For more detailed information on switching or stopping antidepressants see the CKS topic on Depression.

▪ Advise the woman not to stop taking her medication unless otherwise directed by the psychiatrist or, in the case of mild or moderate depression, by the primary care practitioner.

▪ Discuss the standard pre-conception measures (see What to check in all women).

Clarification / Additional information

- **Key symptoms:**

o Persistent sadness or low mood

o Loss of interests or pleasure

o Fatigue or low energy

- **Associated symptoms:**

o Disturbed sleep

o Poor concentration or indecisiveness

o Low self-confidence

o Poor or increased appetite

o Agitation or slowing of movements

o Guilt or self-blame

o Suicidal thoughts or acts

- **Major depression** is diagnosed if the person has four or more of the above symptoms for at least 2 weeks. Major depression is classified according to severity:

o **Mild depression** is diagnosed if the person has four symptoms (at least one key symptom and three associated symptoms). A person with mild depression is generally disturbed but able to carry out normal activities.

o **Moderate depression** is diagnosed if the person has five or six symptoms (at least one of which is a key symptom). A person in this state is likely to have great difficulty continuing with normal activities.

o **Severe depression** is diagnosed if the person has seven or more symptoms (at least one of which is a key symptom), with or without psychotic features. A person in such a state is highly dysfunctional, and often has prominent feelings of worthlessness and guilt, with suicidal thoughts.

[WHO, 1992; NICE, 2004b]

- **For further information, see the CKS topic on Depression.**

Basis for recommendation

- Referral to a psychiatrist is recommended for women with severe depression who wish to become pregnant, as it is important to balance the risk to the fetus from possible drug-related effects against the

risks to both the mother and the fetus from failing to adequately treat the mother's depression, particularly if there is a high risk of self-harm.

- **Tricyclic antidepressants (TCAs)**

o Extensive epidemiological studies have shown no evidence that therapeutic doses of TCAs are associated with an increased incidence of congenital malformations or other adverse pregnancy outcomes [NTIS, 2005c].

- **Selective serotonin reuptake inhibitors (SSRIs)**

o Fluoxetine is the SSRI with most evidence of safety in pregnancy, and remains the first-line SSRI for use during pregnancy [NTIS, 2005a].

o Two recent unpublished studies have raised concerns about a possible increase in the risk of congenital malformations associated with prenatal exposure to SSRIs in general, and more specifically with paroxetine. These studies suggest that in women taking paroxetine in the first trimester, the risk of congenital malformation may increase from 3% to around 4%, with an increase in risk from about 1% to 2% for congenital heart malformations [MHRA, 2005].

- **Monoaminoxidase inhibitors (MAOIs)**

o MAOIs are not recommended for use in pregnancy. There are limited data available on the safety of MAOIs in pregnancy. They can exacerbate pregnancy-associated hypertension, with consequences for fetal growth and development, and they have the potential to interact with other medication and certain food substances, which may produce a hypertensive crisis [Garbis and McElhatton, 2001; NTIS, 2005c].

- **Other antidepressants**

o Other antidepressants (e.g. mirtazapine, reboxetine, venlafaxine) are best avoided as there is little or no experience of their use during pregnancy [Garbis and McElhatton, 2001].

How do I manage a woman with bipolar disorder who wishes to become pregnant?

- **Refer all women with bipolar disorder who wish to become pregnant to a psychiatrist** for assessment of bipolar disorder and review of current medication.

- Advise the woman to continue using effective contraception until she has been fully reviewed by the psychiatrist.

- Advise the woman not to stop taking her medication unless otherwise directed by the psychiatrist.

- Discuss the standard pre-conception measures (see What to check in all women).

o Women taking antiepileptic drugs for treatment of their bipolar disorder are considered to be at high risk of conceiving a child with a neural tube defect, and should be prescribed folic acid 5 mg daily.

Basis for recommendation

▪ Referral to a psychiatrist is recommended to assess and manage the potential risks to both mother and fetus.

o **The potential for medication to cause adverse obstetric and neonatal outcomes** — the National Institute for Health and Clinical Excellence (NICE) recommends that women with bipolar disorder who are considering pregnancy should normally be advised to stop taking valproate, carbamazepine, lithium, and lamotrigine, and that alternative prophylactic drugs (such as an antipsychotic) should be considered.

o **The effect of pregnancy and childbirth on the natural course of bipolar disorder** — in women with a diagnosis of bipolar disorder there is approximately a 50% chance of an episode of psychosis in the postnatal period.

o **The effect of medication on fertility** — conventional antipsychotics and some atypical antipsychotics can reduce fertility by causing hyperprolactinaemia.

[NICE, 2006]

How do I manage a woman with schizophrenia who wishes to become pregnant?

▪ **Refer all women with schizophrenia who wish to become pregnant to a psychiatrist** for assessment of schizophrenia and review of current medication.

▪ Advise the woman to continue using effective contraception until a full assessment by the psychiatrist has taken place.

▪ Advise the woman not to stop taking her medication unless otherwise directed by the psychiatrist.

▪ Discuss the standard pre-conception measures (see What to check in all women).

Basis for recommendation

▪ **Referral to a psychiatrist is recommended** to assess the potential risk to the fetus of current medication, and the likelihood of maternal relapse.

o There is conflicting evidence regarding the teratogenic risks of the older antipsychotic drugs. Case reports of malformations have been reported with the phenothiazines, but most larger studies have not shown a significantly increased risk of malformations. Two old case reports of malformations have been reported following maternal use of haloperidol, but there is no further evidence of its teratogenicity [Garbis and McElhatton, 2001].

o The use of the newer atypical antipsychotics is not recommended during pregnancy as data are lacking [Garbis and McElhatton, 2001].

o In severe or chronic psychosis, it may be preferable to continue maintenance therapy, particularly if the woman has deteriorated in the past when medication has been stopped. This is because increased doses may be needed to treat a relapse of the illness in the event of any medication being stopped [Kumar and O'Dowd, 2001].

How do I manage a woman with epilepsy who wishes to become pregnant?

▪ **Reassure the woman that, even on antiepileptic medication, there is a 90% chance of having a normal pregnancy and delivery.** However, the woman should be informed that the risk of complications during pregnancy and labour is higher than for women without epilepsy.

▪ **Refer all women taking antiepileptic drugs (AEDs) to a specialist** for review of epilepsy treatment *before* the woman becomes pregnant, to discuss the relative risks and benefits of adjusting their medication.

▪ Advise the woman to continue using effective contraception until a full assessment by the specialist has taken place.

▪ Advise the woman not to stop taking her medication unless otherwise directed by the specialist.

▪ Discuss the standard pre-conception measures (see What to check in all women).

o Women taking AEDs are considered to be at high risk of conceiving a child with a neural tube defect, and should be prescribed folic acid 5 mg daily.

Basis for recommendation

▪ These recommendations are consistent with recommendations from the National Institute for Health and Clinical Excellence (NICE) clinical guideline on epilepsy [NICE, 2004a].

▪ Referral is important to assess the risk to the fetus of current medication, and the risk to the mother and fetus of uncontrolled seizures during pregnancy.

o NICE identified five prospective studies that measured changes in the frequency of seizures during pregnancy in women with epilepsy. They concluded that:

o Generally, seizure frequency does not increase during pregnancy or in the early puerperium in women with epilepsy.

o In a minority of women with epilepsy there may be an increase in the frequency of seizures (between 15% and 37%).

o 1–2% of women with epilepsy will have a tonic-clonic seizure during labour, and a further 1–2% within the following 24 hours.

o Pregnancy in women with epilepsy is associated with a higher risk of congenital abnormalities compared with women who do not have epilepsy. However, these malformations are associated with the use of AEDs rather than epilepsy itself.

o The most common major malformations associated with AEDs include neural tube defects, orofacial defects, congenital heart abnormalities, and hypospadias.

o Minor malformations include hypertelorism, epicanthic folds, and digital hypoplasia.

o NICE identified one technology appraisal of the effects of AED treatment during pregnancy. This was based on the outcomes of 2028 pregnancies.

o In women taking one AED the risk of a major congenital malformation was 4% (95% CI 3.2% to 5.3%).

o In women taking more that one AED the risk of a major congenital malformation was 6.3% (95% CI 4.3% to 9.1%).

o All the older AEDs have been associated with malformations. Sodium valproate has been associated with a significantly higher risk of malformations than carbamazepine. There is insufficient data to assess the risks associated with the newer AEDs.

[SIGN, 2003; NICE, 2004a].

How do I manage a woman with thyroid disease who wishes to become pregnant?

Subclinical hypothyroidism:

▪ Perform thyroid function tests (TFTs) before conception if they have not been done in the past 6 months.

▪ If a woman has subclinical hypothyroidism and is not receiving levothyroxine treatment, commence this whilst waiting for specialist referral. Follow local specialist advice regarding an appropriate starting dose.

▪ Advise women who are planning a pregnancy to consult their GP as soon as they think they may be pregnant as dosage adjustment will be needed, together with regular monitoring of thyroid function.

Hypothyroidism:

▪ Ensure optimum control before pregnancy and refer as appropriate.

▪ Perform TFTs before conception if possible, to check adequacy of treatment, and to make sure the woman is stable. Ensure she understands the importance of compliance with levothyroxine therapy.

▪ Advise women who are planning a pregnancy to consult their GP as soon as they think they may be pregnant as dosage adjustment will be needed, together with regular monitoring of thyroid function.

Hyperthyroidism:

▪ Refer women who are not already under consultant care, or inform the specialist responsible for the woman's care that she wishes to conceive.

▪ Advise the woman that frequent monitoring of thyroid function will be required during pregnancy.

▪ Deferring pregnancy until the course of treatment has been completed may be a better option, if practical.

▪ For women planning pregnancy within the next 2–3 years, initial treatment with radioactive iodine or surgery may be best. Radioactive iodine is contraindicated in pregnancy and during breastfeeding —

women should avoid becoming pregnant and men should not father children for at least 4 months following treatment.

- For further details, see the CKS topics on Hyperthyroidism and Hypothyroidism.
- Discuss the standard pre-conception measures (see What to check in all women).

Basis for recommendation

Subclinical hypothyroidism

- These recommendations are based on expert opinion [Edwards and Vanderpump, 2007]. Some of the evidence to support these recommendations is based on observational studies.

o There is evidence that subclinical hypothyroidism can progress to overt hypothyroidism, particularly in people who are antithyroid-antibody positive [Vanderpump et al, 1995; Surks et al, 2004].

o The need for levothyroxine is increased in pregnancy in women with hypothyroidism, and absorption of levothyroxine may be diminished. It is important to intervene quickly [BTA et al, 2006].

o There is evidence of increased fetal loss, and intelligence quotient (IQ) and psychomotor deficits, in infants born to mothers with undiagnosed or inadequately treated hypothyroidism (including subclinical hypothyroidism) [Haddow et al, 1999; Pop et al, 1999; Casey et al, 2005].

o The increase in the levothyroxine dose is necessary to maintain normal serum thyroid stimulating hormone (TSH) and free thyroxine (FT4) for the gestational age [BTA et al, 2006].

Hypothyroidism

- These recommendations are based on a UK consensus guideline produced by the Association for Clinical Biochemistry, British Thyroid Association, and the British Thyroid Foundation [BTA et al, 2006].

o The need for levothyroxine increases in pregnancy in women with hypothyroidism, and absorption of levothyroxine may be diminished. It is therefore important to intervene quickly [BTA et al, 2006].

o The increase in the levothyroxine dose is necessary to maintain normal serum TSH and FT4 for the gestational age. A TSH concentration of 0.4–2.0 mU/L is normal for pregnancy [BTA et al, 2006].

o There is evidence of increased fetal death, and intelligence quotient (IQ) and psychomotor deficits, in infants born to mothers with undiagnosed or inadequately treated hypothyroidism [Haddow et al, 1999; Pop et al, 1999; Casey et al, 2005].

o Other risks include a higher incidence of abortion, stillbirth, pre-eclampsia, prematurity, placental abruption, anaemia, post-partum haemorrhage, cardiac dysfunction, and congenital abnormalities [McGregor, 1996].

o If inadequately treated, hypothyroidism is associated with anovulation. However, with adequate replacement, ovulation is normal [Chamberlain and Morgan, 2002].

Hyperthyroidism

▪ Consensus statement for good practice and audit measures in the management of hypo- and hyperthyroidism recommends that anyone with hyperthyroidism can expect referral to a specialist at diagnosis [Vanderpump et al, 1996]. As hyperthyroidism in pregnancy can present special concerns, the recommendation to inform the woman's specialist is a pragmatic one, in order to address any specific concerns as soon as possible.

▪ Antithyroid drugs (carbimazole or propylthiouracil), at the smallest dose necessary to achieve euthyroidism, are the treatments of choice during pregnancy [Vanderpump et al, 1996]. There is little evidence of teratogenicity, although there is a possible association of carbimazole with fetal aplasia cutis (a rare congenital scalp defect) [O'Doherty et al, 1999; Diav-Citrin and Ornoy, 2002].

▪ Thyroid function will need to be monitored every 4–6 weeks during pregnancy to maintain optimum control as the need for antithyroid treatment often declines through pregnancy, and also because both drugs cross the placenta and over-treatment can adversely affect the fetus [Singer et al, 1995; O'Doherty et al, 1999].

▪ Published evidence suggests that the small risk to the fetus of antithyroid treatment is less than that of untreated or poorly controlled thyrotoxicosis [O'Doherty et al, 1999].

▪ Use of radioactive iodine is contraindicated during pregnancy. Consensus recommends that women of childbearing age should wait at least 4 months after radioiodine treatment before trying to conceive [Vanderpump et al, 1996; O'Doherty et al, 1999].

How do I manage a woman with diabetes who wishes to become pregnant?

▪ **Refer all women with diabetes who wish to become pregnant to a pre-conception diabetes clinic (if available) or to their diabetes care team,** as soon as possible.

o Advise women with type 2 diabetes that their current medication for diabetes will need to be reviewed, and that they will probably be advised to switch to insulin therapy for the duration of their pregnancy.

▪ Discuss the importance of optimal blood glucose control with the woman.

o Women planning pregnancy should aim to achieve a pre-conception glycosylated haemoglobin (HbA_{1c}) value of < 7%.

▪ Advise the woman to continue using effective contraception methods until this target has been achieved.

▪ Ensure that complications of diabetes are reviewed.

▪ Ensure that concurrent medication is reviewed.

▪ Measure thyroid stimulating hormone (TSH), free thyroxine (FT4), and thyroid peroxidase antibodies (TPO-Ab) in women with type 1 diabetes.

▪ Discuss the standard pre-conception measures (see What to check in all women).

o Women with diabetes are considered to be at high risk of conceiving a child with a neural tube defect, and should be prescribed folic acid 5 mg daily.

Clarification / Additional information

Optimal blood glucose control

▪ Women planning pregnancy should aim to achieve a pre-conception HbA_{1c} value of < 7%. Women should aim to achieve HbA_{1c} levels as close to the normal range as possible (where the upper limit of normal in people without diabetes is 6%), whilst avoiding the risk of hypoglycaemia [McIntyre and Flack, 2004; CEMACH, 2006; Diabetes UK, 2006].

▪ Home blood-glucose test results should not be higher than 5.5 mmol/L before meals, and 7.7 mmol/L 2 hours after meals [CEMACH, 2006; Diabetes UK, 2006].

Review complications of diabetes

▪ Arrange screening for retinopathy, nephropathy, and neuropathy [Canadian Diabetes Association and Clinical Practice Guidelines Expert Committee, 2003; International Diabetes Federation, 2005; American Diabetes Association, 2007] (see the CKS topic on Diabetes type 2).

▪ Evaluate cardiovascular disease risk and ensure optimal blood pressure control [International Diabetes Federation, 2005; American Diabetes Association, 2007] (see the CKS topics on CVD risk assessment and management, Hypertension - not diabetic, and Hypertension in pregnancy).

Review concurrent medication

▪ Stop angiotensin converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists (AIIRAs) [International Diabetes Federation, 2005; CEMACH, 2006; American Diabetes Association, 2007] (for details of managing hypertension in pregnancy see the CKS topic on Hypertension in pregnancy).

▪ Stop statins and fibrates [International Diabetes Federation, 2005; CEMACH, 2006].

Basis for recommendation

Referral:

▪ The recommendation to refer all women is based on the Confidential Enquiry into Maternal and Child Health [CEMACH, 2006]. Referral is recommended to explain the risks associated with pregnancy, to ensure that optimal blood glucose control is achieved, and to review any medication that may be harmful to the fetus.

▪ Women with type 2 diabetes who are planning a pregnancy should discontinue oral hypoglycaemics prior to conception (metformin is occasionally indicated) and attain glycaemic targets using insulin, if indicated. This should be done under specialist supervision.

o There is no evidence that metformin or the sulphonylureas are teratogenic. However, metformin may be associated with growth retardation and hyperbilirubinaemia. Sulphonylureas cross the placenta and may cause hyperinsulinaemia and macrosomia in the fetus [Seymour and Pugh, 2000; American Diabetes Association, 2003].

o Insulin allows a better degree of metabolic control during pregnancy than oral hypoglycaemics.

o Human insulin does not cross the placenta, and there is no indication that it is associated with an increased risk of fetal or neonatal toxicity [NTIS, 2005b]. Insulin glargine is not recommended for use during pregnancy as there is currently a lack of data to support its safety [NTIS, 2005b].

Optimal blood glucose control:

▪ The recommendation to aim for a pre-conception HbA_{1c} < 7% is based on recommendations from CEMACH and Diabetes UK.

o **Poor control of diabetes** increases the risks of major congenital abnormality and spontaneous abortion. Studies have identified an association between raised maternal glucose levels during embryogenesis and high rates of spontaneous abortion and major malformation [American Diabetes Association, 2003].

o Observational studies indicate that the risk of malformations increases continuously with increasing maternal glycaemia during the first 6–8 weeks of gestation [American Diabetes Association, 2007].

o Epidemiological studies indicate that HbA_{1c} values less than 1% above normal are associated with rates of congenital malformations and spontaneous abortions similar to those in non-diabetic pregnancies [American Diabetes Association, 2003].

o Studies have shown that providing pre-conception care to promote the achievement of tight blood glucose control during the pre-conception period and the first trimester reduces rates of malformation [American Diabetes Association, 2003].

▪ Pre-conception care appears to reduce the risk of congenital malformations (five non-randomized studies; incidence = 1.0–1.7% in infants of mothers receiving care vs. 1.4–10.9% in women who did not participate) [American Diabetes Association, 2007].

▪ The risk of hypoglycaemia is likely to increase during pregnancy, due to the tight control required to minimize risk to the fetus, and to a decreased awareness of the signs and symptoms of hypoglycaemia [National Diabetes Support Team, 2006].

Review complications of diabetes:

▪ Diabetic retinopathy, if present, can accelerate during pregnancy [Diabetes UK, 2006]. Rapid reduction of blood glucose concentrations has been shown to accelerate diabetic retinopathy in both pregnant and non-pregnant women. There is also evidence that pregnancy, and hypertension complicating pregnancy, may act as independent risk factors for the progression of diabetic retinopathy. Formal retinal assessment should therefore be performed before pregnancy so that improved diabetic control can be achieved in the 3–9 months before a planned conception. This should avoid the need for acute improvement of the blood

glucose concentrations in early pregnancy and thus minimize the risk of exacerbating proliferative retinopathy [Gillmer, 2003; Warrell et al, 2003].

▪ Overt nephropathy is associated with various pregnancy complications, including pre-eclampsia, growth retardation, and fetal distress, but there is little evidence to suggest that pregnancy will hasten the progression of overt nephropathy to end stage renal failure [Gillmer, 2003].

▪ Autonomic neuropathy may complicate the management of diabetes during pregnancy, and these complications should ideally be identified and managed before conception [American Diabetes Association, 2003].

▪ Aggressive monitoring and control of hypertension in the pre-conception period is necessary to reduce the risk of further diabetic complications, and to stabilize the woman's blood pressure on drugs that are safe during pregnancy [American Diabetes Association, 2003].

Review concurrent medication:

▪ Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor blockers should be stopped prior to pregnancy. ACE inhibitors have been associated with fetal growth restriction, inadequate levels of amniotic fluid, neonatal renal failure, and neonatal death [Ramsay et al, 1999; Working Group on High Blood Pressure in Pregnancy, 2000]. On the basis of the experience with ACE inhibitors and data from case studies showing a similar spectrum of toxicity, angiotensin-II receptor antagonists are not recommended for use during pregnancy [NTIS, 2002b].

▪ Statins and fibrates should be stopped prior to pregnancy. The long-term treatment of hyperlipidaemia is not likely to be significantly impaired by temporarily stopping these drugs, and their safety during pregnancy has not been proven [Rost van Tonningen, 2001].

Measure thyroid function:

▪ The recommendations to test thyroid function is based on a UK consensus guideline produced by the Association for Clinical Biochemistry, British Thyroid Association, and the British Thyroid Foundation [BTA et al, 2006]. The strength of evidence supporting this recommendation is expert opinion alone.

o The guideline recommends carrying out thyroid function tests in asymptomatic people only if they are at high risk of having or developing hypothyroidism. In women with type 1 diabetes there is a 5–10% coincidence of hyper- or hypothyroidism [American Diabetes Association, 2003].

How do I manage a woman with chronic cardiac disease who wishes to become pregnant?

▪ **Refer all women with cardiac disease who wish to become pregnant to a cardiologist** for accurate diagnosis and functional assessment so that maternal and fetal risk can be assessed.

▪ Advise the woman to continue using effective contraception until she has been fully assessed.

▪ Discuss the standard pre-conception measures (see What to check in all women).

Basis for recommendation

▪ Up to 10% of maternal deaths in the United Kingdom are a result of heart disease.

▪ All women with chronic cardiac disease should undergo accurate diagnostic and functional evaluation prior to pregnancy, in order to predict maternal and fetal risk as far as possible:

o Women with heart disease and no symptoms (or minimal symptoms) prior to pregnancy will have a relatively low risk of complications during pregnancy and the peripartum period.

o Women with moderate-to-severe limitations are at much higher risk and need careful monitoring and, if necessary, intervention.

o Women who are symptomatic at rest have a high risk of maternal and fetal mortality, and pregnancy is contraindicated until their cardiac function can be improved.

[Forfar, 2003]

How do I manage a woman with chronic hypertension who wishes to become pregnant?

▪ **Refer all women with a history of hypertension who wish to become pregnant to a cardiac specialist** prior to becoming pregnant.

▪ Advise the woman to continue using effective contraception until she has been fully assessed.

▪ Advise the woman not to stop taking her current medication unless otherwise directed by the specialist.

▪ Advise the woman that she will be at increased risk of pre-eclampsia during pregnancy, and that she will require careful monitoring.

▪ Discuss the standard pre-conception measures (see What to check in all women).

Basis for recommendation

▪ **Chronic hypertension is associated with an increased risk of pre-eclampsia, placental abruption, and increased neonatal morbidity and mortality [Sibai et al, 1998].**

▪ The Working Group on High Blood Pressure in Pregnancy recommends that, prior to becoming pregnant, women with a history of hypertension should be reviewed by a cardiac specialist [Working Group on High Blood Pressure in Pregnancy, 2000]. This is in order to:

o Arrange shared care.

o Review the diagnosis — although most women will have essential hypertension, some may have undiagnosed secondary hypertension, which can deteriorate rapidly during pregnancy.

o Review the woman's current medication:

o If the hypertension is mild and well controlled, some specialists may attempt to stop or reduce treatment under close observation.

o If treatment is to be continued, switching to an antihypertensive drug that is thought to be safer during pregnancy might be considered.

o Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor blockers should be stopped prior to pregnancy. ACE inhibitors are associated with fetal growth restriction, reduced amniotic fluid levels, neonatal renal failure, and neonatal death [Ramsay et al, 1999; Working Group on High Blood Pressure in Pregnancy, 2000]. On the basis of the experience with ACE inhibitors and data from case studies showing a similar spectrum of toxicity, angiotensin-II receptor antagonists are not recommended for use during pregnancy [NTIS, 2002b].

o The drugs with most safety data are methyldopa, beta-blockers (labetalol, metoprolol, propranolol), and hydralazine. If these drugs are ineffective, a modified-release preparation of nifedipine may be considered as a second-line alternative [NTIS, 2002a].

[Working Group on High Blood Pressure in Pregnancy, 2000]

▪ **Pre-eclampsia complicates 25% of pregnancies in women with pre-existing hypertension.** The incidence is higher if there is associated renal insufficiency, longer duration (hypertension for 4 years or more), and a history of hypertension in previous pregnancies [Working Group on High Blood Pressure in Pregnancy, 2000].

For further details, see the CKS topic on Hypertension in pregnancy.

How do I manage a woman with renal disease who wishes to become pregnant?

▪ **Women who have renal disease and are planning a pregnancy should be referred to a specialist** for assessment.

▪ Advise the woman to continue using effective contraception until she has been fully reviewed by the specialist.

▪ Discuss the standard pre-conception measures (see What to check in all women).

Basis for recommendation

▪ **Renal disease during pregnancy is associated with risk** of prematurity, intrauterine growth retardation, and accelerated deterioration in maternal renal function [Jungers and Chauveau, 1997].

o **Mild renal disease (serum creatinine < 125 micromol/L)** does not usually worsen during pregnancy, but fetal survival may be moderately reduced.

o **Moderate or severe renal disease (serum creatinine > 125 micromol/L)** may accelerate during pregnancy and jeopardize fetal survival.

o **Most women with serum creatinine greater than 250 micromol/L** are infertile. If they do conceive their chances of a normal pregnancy and a healthy child are low, and the risks to maternal health are high.

▪ If there is associated hypertension before conception or in early pregnancy there is a 10-fold increase in the relative risk of fetal loss.

▪ **Women with renal diseases that tend to progress** should be encouraged to complete childbearing whilst renal function is preserved.

▪ **Women who have had a renal transplant** should be advised to wait 1.5–2 years after the transplant and only attempt pregnancy if creatinine is stable at or below 200 micromol/L. The specialist may also need to change the immunosuppressant medication (tacrolimus and mycophenolate are contraindicated in pregnancy).

[Working Group on High Blood Pressure in Pregnancy, 2000; Firth, 2003]

How do I manage a woman with venous thromboembolism who wishes to become pregnant?

▪ **Screen all women with a personal or an immediate family history of venous thromboembolism (VTE)** for both inherited and acquired thrombophilia. Thromboprophylaxis, either in the first trimester or post-partum, may be required.

▪ **Seek specialist advice** for women who have a past history of deep vein thrombosis or pulmonary embolism, and for those with an abnormal thrombophilia screen.

▪ **Refer all women receiving warfarin therapy who are planning a pregnancy to a specialist** for advice, as warfarin will need to be stopped or replaced by heparin, depending on the woman's degree of risk of VTE.

▪ Discuss the standard pre-conception measures (see What to check in all women).

Clarification / Additional information

▪ Women who are on warfarin and planning a pregnancy should be switched to heparin or low-dose aspirin prior to pregnancy or, at the latest, before the seventh week after conception.

▪ If the woman continues to take warfarin in the pre-conception period, adequate pregnancy testing must be undertaken so that warfarin can be stopped prior to the seventh week.

[Reuvers, 2001]

Basis for recommendation

▪ **Pulmonary embolism is the leading cause of maternal death** in the UK, accounting for one third of all maternal deaths [Bonnar, 2001]. Women with a history of deep vein thrombosis or pulmonary embolism in association with pregnancy, surgery, or the contraceptive pill should be considered especially at risk of

recurrence during pregnancy, whether or not an underlying thrombophilia has been detected [Bonnar, 2001].

- There is some evidence that pregnancy leads to an increase in the risk of venous thromboembolism in women with a previous thrombosis. One retrospective study of women with a history of previous thromboembolism found a recurrence rate of 10.9% per 100 patient-years during pregnancy, compared with a rate of 3.7% in women who were not pregnant [Pabinger et al, 2002].

- **Inherited and acquired thrombophilia** not only increase the risk of venous thrombosis in pregnancy, but may also be partly responsible for recurrent fetal death and intrauterine growth retardation [Bonnar, 2001].

- **Warfarin is teratogenic** and should ideally be stopped before conception and therapy switched to heparin or low-dose aspirin as appropriate. If this is not possible, stopping anticoagulation before the 7th week of gestation may minimize the risk to the fetus [Reuvers, 2001].

How do I manage a woman with asthma who wishes to become pregnant?

- **In women with mild to moderate asthma,** ensure that asthma is well controlled.

- **For women with severe asthma and those in whom asthma is poorly controlled,** refer to a chest physician to ensure adequate control and monitoring.

- Discuss the importance of continuing to take asthma medication as prescribed, both before conception and throughout the pregnancy, to maintain good asthma control.

- Discuss the standard pre-conception measures (see What to check in all women).

Clarification / Additional information

- For further details of asthma management see the CKS topic on Asthma.

- **Treatment of controlled asthma requires little modification in pregnancy.** The risks from uncontrolled asthma are much greater than the risk from asthma treatment during pregnancy.

- **Use beta$_2$-agonists, inhaled or oral corticosteroids, cromones, and theophylline as normal** in pregnancy. Leukotriene receptor antagonists may be continued during the pre-conception period and after conception if they have produced a good response and are considered essential [SIGN and BTS, 2005].

Basis for recommendation

- There is little evidence that pregnancy consistently affects the clinical course of asthma.

- Large epidemiological studies suggest increased risks of pre-term delivery, low birthweight, and congenital malformations in women with asthma compared to those without. These risks are generally

considered to relate to poor control of asthma — studies have shown that when asthma in pregnancy is managed by a respiratory specialist, and good control achieved, there are no additional fetal risks.

▪ There is sufficient experience with beta$_2$-agonists, inhaled corticosteroids, antimuscarinic bronchodilators, cromones, and theophylline to recommend their use as normal during pregnancy [SIGN and BTS, 2005].

▪ There is less experience with leukotriene receptor antagonists during pregnancy, but the Scottish Intercollegiate Guidelines Network and British Thoracic Society (SIGN and BTS) guidelines recommend that they may be continued during pregnancy if they have produced a good response and are considered essential [SIGN and BTS, 2005].

▪ Concerns that oral corticosteroids may be teratogenic and cause facial clefts are not supported by current studies:

o There is also no evidence of suppression of the fetal hypothalamo–pituitary–adrenal (HPA) axis, at least with doses of up to 25 mg prednisolone per day.

o Prolonged exposure increases the risk of intrauterine growth retardation, although it is not clear whether these effects are associated with the maternal illness or are directly related to corticosteroid use.

o Prednisolone is the preferred oral corticosteroid as it is extensively metabolized by placental enzymes and little crosses the placenta.

[de Swiet, 2003]

How do I manage a woman with rheumatoid arthritis who wishes to become pregnant?

▪ **Refer all women with rheumatoid arthritis who wish to become pregnant to a rheumatologist,** especially if they are taking nonsteroidal anti-inflammatory drugs (NSAIDs) or disease-modifying anti-rheumatic drugs (DMARDs).

▪ Ensure the use of effective contraception whilst taking DMARDs. Because of their long half life, some DMARDs may need to be discontinued several months before a planned conception.

▪ Discuss the standard pre-conception measures (see What to check in all women).

Basis for recommendation

▪ **Referral to a rheumatologist is recommended** for a review of the woman's medication. The main concerns relate to the safety during pregnancy of some drugs used to control rheumatoid arthritis.

▪ Because of the teratogenic and fetotoxic effects of many DMARDs, women should be advised to continue using effective contraception until their medication has been reviewed, and in some cases for several months after stopping medication.

How do I manage a woman with sickle-cell disease who wishes to become pregnant?

▪ **Refer all women with a sickle-cell disease to a haematologist** for assessment and explain that regular monitoring during pregnancy will be essential.

▪ Advise the woman to continue using adequate contraception until the disease status has been fully assessed by a haematologist.

▪ Women who are carriers should be treated as for a normal pregnancy.

▪ Discuss the standard pre-conception measures (see What to check in all women).

o Women with homozygous sickle-cell disease (HbS/S) and sickle-cell haemoglobin C disease (HbS/C) disease should take folic acid 5 mg daily for life.

o Women who are sickle-cell carriers (HbS/A) should receive folic acid 400 micrograms daily.

Clarification / Additional information

▪ Ideally pregnant women with sickle-cell disease should be managed by a team that includes a haematologist and an obstetrician with experience and expertise in managing sickle cell patients. This will depend on local availability.

Basis for recommendation

▪ **Homozygous sickle-cell disease (HbS/S):** pregnancy may be uneventful, or may be associated with an increased incidence of painful crises. Abortion and preterm loss are more common than in a normal pregnancy. Although risks remain higher for women with sickle-cell disease, modern obstetric care has reduced both maternal morbidity and mortality, and has improved fetal outcome.

▪ **Sickle-cell haemoglobin C disease (HbS/C):** many women have uncomplicated pregnancies, but a severe sickling crisis can occur in pregnancy or early in the puerperium.

▪ **Sickle-cell carriers (HbA/S):** women have no problems from overt sickling during pregnancy, but care is needed to avoid hypoxia if a general anaesthetic is required.

[Warrell et al, 2003]

How do I manage a woman with thalassaemia who wishes to become pregnant?

▪ **Refer all women with thalassaemia to a haematologist** for assessment.

▪ **Women who are carriers:**

o Seek advice from a haematologist or haemoglobinopathy counsellor (if available) for women who are carriers and have an unusual variant or need further investigation.

o Ensure that the woman's partner has been tested (see Advice when risk of genetic disorder).

- Discuss the standard pre-conception measures (see What to check in all women).

o Women with thalassaemia should receive folic acid 5 mg daily throughout the pregnancy.

o There is also some evidence to suggest that women who are carriers should receive folic acid 5 mg daily throughout the pregnancy.

Basis for recommendation

- **Alpha-thalassaemia carriers:** the woman may become anaemic particularly if she is a carrier of two defective genes [Letsky, 1999].

- **3-alpha-thalassaemia (HbH disease):** the woman will have chronic haemolytic anaemia and may require transfusion [Letsky, 1999].

- **Homozygous alpha-thalassaemia** (Bart's haemoglobin hydrops syndrome): pregnancy is associated with severe, sometimes life-threatening pre-eclampsia. Vaginal deliveries are often associated with obstetric complications resulting from the large fetus, bulky placenta, and often the small stature of the mother (usually of Far Eastern origin) [Letsky, 1999].

- **Beta-thalassaemia minor** (symptomless carriers): if iron stores are depleted, the woman may need oral iron supplements during pregnancy. Before giving iron supplements it is important to confirm with the local haematologist that the woman is truly iron-deficient. A low mean cell volume (which is a feature of beta-thalassaemia) does not usually mean the woman is iron deficient [Letsky, 1999]. Primary care practitioners should request a serum ferritin for these women.

- **Beta-thalassaemia major** (homozygous beta-thalassaemia): pregnancy is rare in these women and is likely to have serious complications [Letsky, 1999]. These women need specialist reproductive endocrinological referral if they wish to become pregnant.

What advice can I give older women who are planning a pregnancy about their risks of having a baby with a chromosomal abnormality such as Down's syndrome?

- **Advise women planning pregnancy who are concerned about the risks of chromosomal abnormalities, such as Down's syndrome and Edward's syndrome, that the risk increases with maternal age** and after a previously affected pregnancy.

- **Advise that there is no pre-conception test** that can predict whether a couple will conceive a baby with a chromosomal abnormality such as Down's syndrome.

- **Advise that antenatal screening tests can estimate the likelihood of a pregnant woman carrying a baby with Down's syndrome.**

- **Advise that a definitive diagnostic test for Down's syndrome is offered to pregnant women at high risk.** This can be established by amniocentesis, chorionic villus sampling, or fetal blood sampling. It is

important that the couple is aware that testing carries a risk of fetal death but this occurs in less than 1% of cases.

Clarification / Additional information

▪ The risk of Down's syndrome increases with maternal age Table 1 [Cuckle et al, 1987]:

Table 1. Risk of Down's syndrome with increasing maternal age.

Age of mother	Risk
20 years	1:1500
30 years	1:800
35 years	1:270
40 years	1:100
45 years and over	1:50 and greater

▪ There is no test that can be done prior to conception to identify when chromosomal abnormalities, such as Down's syndrome, will occur because the chromosomal make-up of both the mother and the father is normal. These disorders are caused by the faulty inheritance of an extra chromosome, from either the mother or the father, that occurs spontaneously at the time of conception.

Basis for recommendation

Basis for advice about risk of Down's syndrome and maternal age:

▪ There is well-established evidence from large epidemiological studies of the relationship between maternal age and the risk of Down's syndrome [Cuckle et al, 1987].

Basis for advice about antenatal screening and diagnosis of Down's syndrome:

▪ These recommendations are derived from a national guideline produced by the Royal College of Obstetricians and Gynaecologists [National Collaborating Centre for Women's and Children's Health, 2003].

What pre-conception advice can I give to a couple who are at a higher risk of having a baby with an inherited genetic disorder including haemoglobinopathies?

Screening for sickle-cell anaemia and thalassaemias (haemoglobinopathies):

▪ Offer haemoglobinopathy screening to all women prior to conception by asking them to complete a family of origin questionnaire (pdf) and send this with blood samples for testing:

o Take blood for full blood count and electrophoresis:

o From all women from high prevalence areas.

o From all women from low prevalence areas if they or their partner come from a population (identified by the questionnaire) at increased risk of haemoglobinopathies.

o Take blood for full blood count alone:

o From women from low prevalence areas who come from a population (identified by the questionnaire) at low risk of haemoglobinopathies.

▪ Screen men for haemoglobinopathies only if the women is identified as a carrier.

Genetic screening for conditions other than haemoglobinopathies:

▪ **Offer referral for genetic screening and counselling to couples that are planning pregnancy who:**

o Have a personal or family history of an inherited genetic disorder.

o Have had a previous pregnancy affected by an inherited genetic disorder.

o Are Ashkenazi Jews (for Tay–Sachs screening).

Pre–natal diagnosis for people known to be carriers of an inherited genetic disorder:

▪ **Offer genetic screening** to the partners of people known to be carriers for recessively inherited genetic disorders. Ideally this should be carried out before the women becomes pregnant.

▪ **Offer referral for pre-natal diagnosis testing** to a women when she is known to be a carrier of a recessively inherited genetic disorder and:

o The father of the baby is known to be a carrier for the same disorder.

o The carrier status of the father is unknown and cannot be established.

▪ **Advise women who would consider termination of an affected pregnancy** that it is important that they present early in pregnancy, ideally before 10 weeks, if they want to avoid a termination after the first trimester.

Clarification / Additional information

Cousin marriage:

▪ The indications for screening for a specific genetic disorder are determined by the population a couple comes from and their personal and family history.

▪ Cousin marriage increases the risk of a couple having a child with a genetic disorder but it does not alter the indications for screening.

Haemoglobinopathy screening:

▪ The family of origin questionnaire should be sent off with blood samples to aid in interpretation of results for all people.

▪ High and low prevalence areas — a general practice should be informed by their hospital trust if they have a population that is at high risk or low risk of haemoglobinopathies.

▪ Further information about haemoglobinopathy screening is available at www.sickleandthal.org.uk (pdf).

Referral for genetic testing:

▪ The most common genetic disorders requiring referral for genetic screening are included in Table 1.

Table 1. Most common genetic disorders requiring referral for testing.

Genetic disorder	Condition
Dominantly-inherited disorders	Neurofibromatosis
	Tuberous sclerosis
	Huntington's disease
	Adult polycystic disease
	Marfan's syndrome
	Achondroplasia
Recessively-inherited disorders	Haemoglobinopathies
	Cystic fibrosis
	Tay–Sachs disease
	Gaucher's disease
	Congenital adrenal hyperplasia
	Friedrich's ataxia
	Spinal muscular atrophy
X-linked disorders	Duchenne's muscular dystrophy
	Fragile X syndrome
	Haemophilias A and B
	Glucose-6-phosphate dehydrogenase deficiency

[Farndon and Kilby, 1999]

Pre–natal diagnosis:

▪ Pre–natal diagnosis is considered appropriate when the risk of a baby being effected by the disorder is high and the women would consider termination of an effected pregnancy.

o For a couple who are both carriers of a recessively inherited genetic disorder the chances of having an effected pregnancy are one in four.

o When only the carrier status of the women can be established the risk of an effected pregnancy will depend on the prevalence of the disorder in a population. For certain high prevalence disorders the risk of an effected pregnancy may be high enough to justify offering pre–natal diagnosis even when the carrier status of the man cannot be established.

o For people who would not find late termination of pregnancy acceptable it is important that they are referred to a fetal medicine specialist early in pregnancy, ideally by 10 weeks to allow time for testing of the father of the baby (if necessary) and pre–natal diagnosis testing prior to termination.

o Pre–natal diagnosis can be carried out from twelve weeks of pregnancy onwards.

Basis for recommendation

- **Screening for haemoglobinopathies and Tay–Sachs disease is recommended by the National Screening committee and NHS Sickle Cell and Thalassaemia Screening Programme.**

o The National Screening committee have set out criteria for when screening is considered appropriate [UK National Screening Committee, 2006]. Based on these criteria the UK National Screening Committee recommend:

o Antenatal screening for haemoglobinopathies for people from high prevalence areas and people from high risk populations.

o Carrier testing and antenatal screening for Tay–Sachs disease in people of Jewish origin.

o The NHS Sickle Cell & Thalassaemia Screening Programme indicate that screening for haemoglobinopathy carrier status may also be considered pre-conception [NHS Screening, 2006].

- People who have a personal or family history of an inherited genetic disorder and people who have previously had an affected pregnancy, are at high risk of having a baby with an inherited genetic disorder. Screening people at high risk is a common sense recommendation supported by experts [Cunniff and American Academy of Pediatrics Committee on Genetics, 2004].