



PRESCRIBING IN PREGNANCY (1)

- 👉 During pregnancy, up to 90% of women take medicines
- 👉 The risks and benefits of treatment must be carefully considered before prescribing in pregnancy, especially in the first trimester
- 👉 Inadequate pharmacological treatment of a condition may cause harm to the mother and fetus
- 👉 Pre-conception advice on the avoidance of teratogenic medicines, the use of folic acid and the need to update vaccinations is important
- 👉 The dose and appropriateness of medicines should be reviewed in women on long-term medications who become pregnant

INTRODUCTION

Up to 90% of women use at least one medicine during pregnancy (prescribed or over the counter [OTC]) and almost half of all women use four or more medicines during their pregnancy.¹⁻⁵ The use of medicines in pregnancy has increased over the last 40 years; this may be due to several factors, such as the increasing rates of pregnancy in older women and the prevalence of co-morbidities requiring pharmacological therapy (e.g. hypertension and diabetes).^{1,6} While medication use during pregnancy may have potential adverse effects on the fetus, the avoidance of all medicines during pregnancy is unrealistic.^{3,7,8} **Inadequate pharmacological treatment of an underlying disease may be more detrimental to the health of the mother and fetus than the medicines used to treat the condition;**^{3,7,8} for example, evidence suggests that poor asthma control during pregnancy increases the risk of pre-eclampsia, low birthweight and prematurity.⁶ Similarly, poorly controlled inflammatory bowel disease (IBD) in pregnancy is associated with an increased risk of prematurity and fetal loss.^{9,10} The majority of medicines are not licensed for use in pregnancy, as medicines are not evaluated in pregnant women prior to being placed on the market.¹¹ The Summary of Product Characteristics is generally regarded as being very conservative in terms of its advice about the use of a medicine in pregnancy.¹² Information on the use of medicines in pregnancy mainly comes from observational sources, which may lack information on confounding factors and be subject to bias.^{1,6} Confounding factors include the therapeutic indication for which the medicine is prescribed, maternal age, co-morbidities, poor obstetric history, concomitant use of other medicines, smoking, alcohol, use of illicit drugs and quality of antenatal care.⁶

A frequent problem facing prescribers is the lack of information on the risks and benefits of using medicines in pregnancy, in particular newer medicines.⁶ The National Medicines Information Centre (NMIC) clinical enquiry answering service commonly receives enquiries on the use of medicines in pregnancy. **This, the first of 3 bulletins, will provide an overview of the principles of prescribing in pregnancy** and highlight useful resources for healthcare professionals. The next 2 bulletins, which will update previous bulletins on this topic, will address frequently asked questions on this subject received by the NMIC.

TERATOGENIC EFFECTS OF MEDICINES

All pregnancies carry risks of adverse outcomes; approximately 15 to 20% of pregnancies result in spontaneous miscarriage and 2 to 3% of live births are associated with a congenital anomaly.^{4,6,8,13,14} The majority (70%) of congenital anomalies are due to unknown causes, 20% have a clear genetic or chromosomal abnormality and 10% have an exogenous cause (e.g. maternal diabetes, rubella, alcohol abuse or use of medicines).^{13,14} Although current **evidence suggests that only approximately 1% of birth defects (affecting <0.2% of all live births) are caused by medicines,**^{8,13,15} it is important to consider the potential risks of all medicines used during pregnancy.⁸

A teratogen is defined as any agent (including a medicine) that results in structural or functional abnormalities in the fetus, or in the child after birth as a result of maternal exposure to the agent during pregnancy.⁸ The teratogenic effects of a medicine may be due to direct effects on the fetus and/or as a consequence of indirect physiological changes in the mother and fetus.^{6,8} Exposure to a teratogen in pregnancy may result in spontaneous abortion or stillbirth, congenital anomalies obvious at birth

(as seen with thalidomide, isotretinoin, methotrexate and mycophenolate mofetil), intrauterine growth retardation, neonatal toxicity or the emergence of delayed childhood developmental effects (as seen with sodium valproate).^{4,8,14,16-18} **The highest risk period for congenital anomalies is during the first trimester** when most organs and systems develop, however **medicines may affect the fetus at any stage of pregnancy.**^{4,6,8} Effects on the growth and development of the fetus may occur as a result of exposure in the second and third trimesters (e.g. the use of angiotensin converting enzyme inhibitors in these trimesters may result in oligohydramnios and fetal renal failure).^{4,6,8} Exposure near term carries the greatest risk of producing adverse functional neonatal effects, such as neonatal toxicity following maternal prescription of opioid analgesics or neonatal adaptation syndrome following maternal use of selective serotonin reuptake inhibitors (SSRIs).^{6,19} Non-steroidal anti-inflammatory drugs (NSAIDs) are another important group of drugs that may cause problems if used in the third trimester e.g. premature closure of the fetal ductus arteriosus and fetal renal impairment.⁸

Congenital anomalies are thought to occur following exposure to a teratogen above a threshold concentration during a time period critical for development of the relevant organs;^{4,6,8} the dosage and duration of a medicine used during pregnancy should be considered.⁴

PHYSIOLOGICAL CHANGES IN PREGNANCY

A number of physiological changes occur during pregnancy which can affect the pharmacokinetics of medicines.^{4,8,20,21} Alterations in the pharmacokinetics of medicines are influenced mainly by two factors: 1) maternal physiological changes and 2) the effects of the placental-fetal compartment.²¹

In pregnancy, there is an increase in the total body water by up to 8 litres; this provides an increased volume in which medicines can be distributed in the mother.^{4,8,20} Other maternal pharmacokinetic changes that occur during pregnancy include **variable effects on hepatic metabolism of medicines.** There may be increased activity of cytochrome P450 (CYP) 3A4, CYP2D6, CYP2A6 and CYP2C9, which may lead to reduced plasma concentrations of medicines (e.g. methadone), while there is reduced activity of CYP1A2 and CYP2C19, which may lead to increased plasma concentrations (e.g. citalopram).^{1,6,8} In addition there is **increased renal blood flow and increased glomerular filtration rate (by 50%) which may lead to a significant increase in the elimination of renally cleared medicines** (e.g. metformin, cefuroxime and gentamicin);^{6,8,22,23} higher doses of these medicines may be required during pregnancy.

Maternal and fetal medicine concentrations are dependent on placental transfer of the medicine, the extent of metabolism by the placenta and fetus and elimination of the medicine from the fetus.²¹ **Most medicines have a low molecular weight and cross the placenta by diffusion.**^{20,21} Highly protein bound and large molecular weight medicines do not cross the placenta (e.g. insulin and heparin).^{20,21} Although the fetal liver and placenta can metabolise medicines, medicines can accumulate in the fetus due to limited metabolic enzyme activity.^{20,21} Medicines are mainly eliminated from the fetus by diffusion back to the mother, however as the fetal kidney matures, metabolites are excreted into the amniotic fluid.²¹

PRE-CONCEPTION ADVICE

It is accepted that up to 50% of pregnancies may be unplanned.^{6,8,24} A delay in the recognition of pregnancy increases the risk of continuing exposure to teratogens in the first trimester, especially for medicines prescribed for chronic conditions.^{6,8} **Therefore it is important to be aware of the potential teratogenic risks associated with individual medicines when prescribing for women of reproductive potential.**⁸ For example, recent advice from the European Medicines Agency, recommends that sodium valproate (Epilim®) is contraindicated in women of childbearing potential, unless all the conditions of the Valproate Pregnancy Prevention Programme are met (see www.hpra.ie/valproate for more details regarding this).¹⁶ **Specialist advice may be required for women with chronic conditions (e.g. epilepsy, diabetes, hypertension, IBD and rheumatoid arthritis), prior to planning a pregnancy, to explore options to reduce the dose or change a medicine if appropriate.**^{3,24-26} However in certain conditions (e.g. depression), changing to an alternative medicine may not always be a safer option, where there is a risk of relapse occurring in well controlled patients, potentially resulting in adverse outcomes.³

Folate supplementation prevents the occurrence of neural tube defects (NTD), which complicates 1 in 1,000 pregnancies in Ireland.²⁷⁻²⁸ Studies suggest that most women do not start folic acid until their pregnancy test is positive which is around the time that the neural tube closes.²⁷⁻³¹ Factors associated with folic acid uptake include higher socioeconomic status, higher maternal age, nulliparity and history of infertility treatment.^{27,28,31} **Women planning a pregnancy should be advised to take folic acid prior**

to conception (at least 1 month), and for up to 12 weeks of pregnancy to prevent NTD.^{8,27,30,32,33}

The dose of folic acid is usually 400 micrograms/day, however a dose of 5 mg/day is recommended for women at high risk of NTD; risks include a previous history of an infant with a NTD, use of medicines including antiepileptics and sulfasalazine, history of diabetes, obesity and sickle-cell disease.^{10,32,34} There is also evidence to support the **continuation of folic acid** after the first trimester in order to reduce the risk of anaemia and need for blood transfusion.^{30,33-35}

The need for vaccination (including hepatitis B, measles, mumps, rubella, varicella, diphtheria, tetanus and pertussis) should be assessed prior to conception.^{8,36,37} For example, serological testing for hepatitis B and varicella can be undertaken if previous vaccination history or infection is uncertain.^{36,38} Two doses of MMR vaccine (one month apart outside of pregnancy), should be offered for women without documented evidence of measles vaccination.³⁶

Women should also be advised to avoid recreational drugs, “natural” or herbal remedies, alcohol, and smoking.^{8,14} Table 1 summarises the advice for a woman planning a pregnancy.

Table 1: Advice for a woman planning a pregnancy^{3,6,8,24,30,33}

Pre-pregnancy advice includes:

- The avoidance of teratogenic medicines prior to conception and during the pregnancy
- To inform their doctor before starting any medicine including over the counter (OTC) before and during pregnancy
- Folic acid supplementation at the appropriate dose at least 1 month prior to conception and for 12 weeks of pregnancy to prevent neural tube defects and throughout pregnancy to reduce anaemia
- Vaccination against infectious diseases in women lacking immunity (e.g. measles, mumps, rubella)
- The avoidance of recreational drugs, “natural” or herbal remedies, alcohol, and smoking
- Specialist input may be required for women with chronic conditions (e.g. epilepsy)

Pre-conception advice for males

It has been hypothesised that male exposure to teratogens including medicines, could potentially increase the risk of fetal malformations.³⁹ In general, paternal exposure to medicines is considered unlikely to cause fetal effects, however medicines that induce genetic alterations in sperm, could theoretically increase the risk of an adverse outcome.^{20,39} The effects of paternal exposure on the fetus for most medicines has not been studied, however the limited data that is available does not suggest a major increased risk to the fetus for medications with genotoxic effects.³⁹ Available evidence does not suggest that peri-conception paternal exposure to medications such as mycophenolate mofetil, azathioprine and methotrexate, which may be present in seminal fluid, results in teratogenic effects.³⁹⁻⁴¹ However, as the data is limited, **prevention of pregnancy is generally advised for men who are exposed to cytotoxic or genotoxic substances and for two sperm cycles (approximately 6 months) after the medicine is discontinued**; this recommendation may vary and specialist advice should be considered for individual patients.³⁹⁻⁴¹

USE OF MEDICINES IN PREGNANCY

From the evidence available, it appears that the majority of medicines used during pregnancy are associated with substantial experience of safety, but prescribing of medicines known to be associated with fetal risks also occurs.^{1,3,6,8,42} A European study found that the majority of pregnant women (69%) used medicines that were considered safe to use in pregnancy (e.g. paracetamol, alginate acid), however 28% used medicines that were classified as potentially risky (e.g. ibuprofen, metoclopramide and codeine).³ Indications for using medicines in pregnancy range from chronic conditions such as depression and epilepsy to possible pregnancy-associated conditions such as hypertension, urinary tract infections and gastro-intestinal complaints.^{1,3,6-8,20} **The greatest likelihood for being prescribed a potentially risky drug in pregnancy is having a chronic condition**; there is an almost four-fold increased likelihood compared to women without a chronic condition.³

The risk to the fetus needs to be evaluated in terms of the benefits of the medicine both to the mother and fetus, versus the risks of withholding treatment.^{6,43} **In certain conditions the benefits of treatment for the mother and fetus outweigh the risks.**^{6,20} For example, women with diabetes mellitus are at increased risk of adverse maternal and fetal outcome; these risks are decreased in diabetic women who achieve good glycaemic control before conception and throughout pregnancy.⁶ Other conditions where the benefits of treatment in pregnancy outweigh the risks include asthma, epilepsy, rheumatoid arthritis, IBD and depression.^{8,10,20,25,26}

Vaccines in pregnancy are recommended when the benefits of protection from vaccination outweigh the risks.³⁶ Seasonal influenza vaccine is recommended for women at any stage in pregnancy; influenza occurring during pregnancy is associated with increased maternal complications and premature birth

and reduced fetal growth.³⁶ Pertussis vaccine is also recommended for all pregnant women between 16 to 36 weeks gestation to reduce the risk of maternal infection and to reduce the risk of infection in infants.³⁸ **All live vaccines are generally contraindicated during pregnancy.**³⁶

Evidence suggests that physicians and pregnant women have unrealistically high perceptions of the teratogenic effects of medicines, which may lead to suboptimal treatment of conditions in pregnancy.^{15,44,45}

PRACTICAL ASPECTS TO PRESCRIBING IN PREGNANCY

Table 2 summarises the principles which should be considered when prescribing during pregnancy.

Table 2: General principles for prescribing in pregnancy^{4,6,8,20}

General principles include:

- The risk/benefit ratio for the mother and fetus should be assessed before prescribing a medicine
- The pregnant woman should be advised of the benefits and risks of the medicine
- A medicine should be prescribed only where there is a clear indication especially in the first trimester, when exposure is most likely to be associated with an increased risk of congenital anomaly; fetal adverse effects may also be associated with exposure in the second or third trimesters
- Medicines with the best known safety profile should be used; newer medicines should be avoided if possible
- The lowest effective dose should be prescribed for the minimal time required
- For medicines subject to therapeutic drug monitoring, plasma concentrations should be measured regularly and the results used to inform dose adjustments
- Polypharmacy should be avoided as far as possible
- Appropriate folic acid supplementation should be advised

SUMMARY

If possible, medicines should be avoided in the first trimester which is associated with the highest risk of congenital anomaly.^{8,20} Specialist input should be sought for chronic conditions including epilepsy, depression and hypertension. Patients should be informed of the benefits and risks of the use of the individual medicines. **Drugs which have been used extensively in pregnancy are preferred to newer drugs**, which should be prescribed at the lowest effective dose.^{6,8,20} If possible, monotherapy is preferred.^{6,8,20} Changes in dosing may be required depending on how the drug is metabolised and/or excreted by the kidneys.⁸

The next two bulletins will deal with specific topics received by the NMIC clinical answering service including the use of antidepressants, antihypertensives, antimicrobials, analgesics and anti-emetics.

USEFUL RESOURCES

- The National Clinical Programme for Obstetrics and Gynaecology has produced guidelines on the management of common and serious conditions available on www.rcpi.ie and www.hse.ie
- Best Use of Medicines in Pregnancy (BUMPs) information leaflets for patients and healthcare professionals available on www.medicinesinpregnancy.org/
- UK Teratology information service (subscription required for full monographs) available on www.uktis.org/
- MotherToBaby is a US teratology information website which provides information for patients and healthcare professionals <https://mothertobaby.org/>
- The Motherisk Program at The Hospital for Sick Children (based in Canada) has information on their website www.motherisk.org/
- The Summary of Product Characteristics (SmPC) for individual medicines is available on www.hpra.ie and www.medicines.ie
- The NMIC clinical enquiry answering service is available to deal with specific enquiries on use of medicines in pregnancy: e-mail nmic@stjames.ie or telephone **01 4730589**

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List of references available on request. Date of preparation: June 2018

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the individual Summary of Product Characteristics (SmPC) for specific information on a drug.

Final references – pregnancy bulletin 1

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