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FREQUENTLY ASKED QUESTIONS ON USE OF MEDICINES IN PREGNANCY (2)

-  Women of reproductive age on chronic therapy should have their therapy reviewed if they intend to become pregnant
-  Older medicines, for which there is more experience of use in pregnancy, are preferred to new or untried drugs whenever possible
-  Stopping chronic therapy during pregnancy may adversely affect the baby
-  When chronic therapy is needed, the importance of compliance to the baby's well-being should be explained to the mother

SECTION 2: FREQUENTLY ASKED QUESTIONS (CONTD.)

What is the treatment of choice for urinary tract infection during pregnancy?

Pregnant women are at increased risk of urinary tract infections (UTIs) compared with non-pregnant women, due to the anatomical and hormonal changes of pregnancy. UTIs are classified according to the site of infection: bacteriuria (urine), cystitis (bladder) or pyelonephritis (kidney).¹ The incidences of asymptomatic bacteriuria (ASB) and acute cystitis during pregnancy are 2-10% and 1-4% respectively. Acute pyelonephritis occurs in 1-2% of pregnant women; the incidence is highest at the end of the second and beginning of the third trimesters.^{1,2} Pyelonephritis can result in pre-eclampsia, gestational hypertension, anaemia, thrombocytopenia, transient renal insufficiency, postpartum endometritis, sepsis, disseminated intravascular coagulation and acute respiratory distress syndrome in the mother. Increased risks for the foetus include premature delivery, low birth weight and foetal mortality.^{1,3} Screening for ASB by urine culture is recommended at the first antenatal visit, as treatment of ASB significantly decreases the incidence of pyelonephritis, and its associated complications.^{4,6} If ASB is left untreated, 20-30% of pregnant women will develop acute pyelonephritis.⁷

Management Options: In ASB, a positive urine culture should be confirmed with a second culture, and the urine culture should guide the choice of antibiotic.^{4,5} Antibiotic treatment of cystitis is usually empiric, although therapy should be tailored to the specific organism once results from culture and sensitivities are available.^{5,8} Penicillins and cephalosporins are usually considered safe for use during pregnancy.^{9,10} **A 7-day course of treatment with amoxicillin, cefalexin or nitrofurantoin is usually recommended for ASB or cystitis,**⁵⁻⁷ although amoxicillin is associated with increasing rates of resistant *E. coli*.^{2,7,11} **Nitrofurantoin should be avoided in the third trimester, due to a risk of neonatal haemolysis.**^{5,11,12}

Early aggressive treatment of pyelonephritis is important, and involves hospitalisation, with administration of parenteral (followed by oral) antibiotic therapy and adequate intravenous hydration.^{1,3,5,7}

There is a diversity of opinion regarding the use of trimethoprim during pregnancy. **In general, it is recommended that trimethoprim should be avoided in pregnancy, particularly in the first trimester.**^{7,9,11} However, current Guidance from Prodigy in the UK suggests that trimethoprim might be considered as a treatment option for empiric therapy of cystitis.⁵ Trimethoprim is a folate antagonist therefore it should be avoided in women with established folic acid deficiency or low dietary folic acid intake, or in those who are taking a folate antagonist, unless a folate supplement is taken.^{5,13}

Follow up of treatment: Urine culture should be undertaken one week after completing treatment of a UTI to ensure response, and then monthly for the remainder of the pregnancy to monitor for recurrence.²⁻⁵ After completion of the primary treatment, pregnant women who have had an episode of acute pyelonephritis or those who have recurrent UTIs should be considered for prophylactic antibiotic therapy.^{7,11} Specialist advice should be obtained with regard to prophylactic antibiotics.⁵

What is the safest analgesic in pregnancy?

No analgesic is without risk when used during pregnancy. The level of risk depends on the stage of pregnancy and the duration of analgesic consumption. There is much experience with the use of **paracetamol** and epidemiological studies have not indicated any embryotoxic action.¹⁴ It has been routinely used at all stages of pregnancy for both pyrexia and pain relief.^{14,15,16} A study was published a number of years ago which suggested that there may be a possible association between frequent use of paracetamol in later pregnancy and the risk of wheezing in children.^{17,18} Therefore, while recognised as being the analgesic of choice during pregnancy, it should not be taken unnecessarily and the use of high doses or prolonged exposure should be avoided.¹⁹

Non-steroidal anti-inflammatory drugs (NSAIDs): The main concerns with NSAIDs relate to use in the latter stages of pregnancy.^{11,14,15,20} NSAIDs when used after 30 weeks of pregnancy are associated with an increased risk of premature closure of the foetal ductus arteriosus, oligohydramnios and possible persistent pulmonary hypertension of the newborn as a result of inhibitory effects of NSAIDs on prostaglandin activity.^{11,14} While most manufacturers of NSAIDs recommend that use during pregnancy be avoided unless the potential benefits outweigh the risks during the first and second trimesters of pregnancy, ibuprofen would be the preferred agent, at the lowest dose for the shortest time period, if a NSAID is required.^{11,14,15,20} In circumstances where the clinical condition requires treatment with NSAIDs during the third trimester, the foetus should be monitored regularly to detect any potential adverse effects.²⁰ **The use of selective COX-2 inhibitors is contraindicated during pregnancy due to a lack of safety data.**^{21,22}

Opioid analgesics can be used during pregnancy; however they have the potential to cause dependence and withdrawal symptoms in the neonate particularly if used at high doses, near term or regularly during pregnancy.^{14,15} Most experience is with **codeine**, which has been used for mild-moderate pain and as an anti-tussive for many years despite limited data on its effects in either animal or human pregnancy. Reports of malformations have been inconsistent and are not believed to indicate an increase in risk.²³ Opioids may be used at any stage of pregnancy for the short-term treatment of moderate to severe pain.¹⁵ With exposure in the third trimester there is particular risk, in addition to withdrawal effects, of neonatal respiratory depression and risk of inhalation pneumonia in the mother during labour. It has been suggested that **tramadol** is embryotoxic in animal studies⁷ and therefore its use is not recommended.

How can heartburn/ gastro-oesophageal reflux be managed in pregnancy?

Gastro-oesophageal reflux and heartburn are extremely common during pregnancy, especially during the later stages of pregnancy. Simple measures such as avoiding 'trigger' foods, not eating close to bedtime, sleeping with extra pillows, and trying to avoid stooping may help relieve symptoms.²⁴ In mild cases lifestyle and dietary modifications alone may be all that is required to improve the symptoms sufficiently.²⁵ **If medicinal treatment is indicated, first-line therapy includes antacids / alginates or sucralfate.**^{25,26} Although antacids and sucralfate may be used at any time during pregnancy, the unlimited use of antacids during pregnancy is not recommended. Among the aluminium-containing antacids, magaldrate (aluminium-magnesium complexes) and sucralfate may be considered the medicines of choice because of their apparently limited aluminium absorption.²⁵ Aluminium salts tend to cause constipation and magnesium salts tend to cause diarrhoea so combining the two can balance these effects.²⁷ Products with high sodium content should be avoided, because they can increase blood pressure.²⁷

H₂-antagonists may be prescribed only when antacids and sucralfate have failed.^{25,26} **Ranitidine is the best studied agent** and may be preferable to cimetidine because of a theoretical concern about the anti-androgenic properties of cimetidine.²⁵

Proton-pump inhibitors (PPIs) should be prescribed during pregnancy only when antacids, sucralfate and ranitidine are not effective. In such a case, **omeprazole, which is the compound with the largest experience in this group, should be chosen.**^{25,26} The limited data do not indicate an increased risk of adverse foetal effects following *in utero* exposure to omeprazole.²⁶ Experience with the use of other PPIs in pregnancy is very limited and insufficient for a well-grounded risk assessment. The Summaries of Product Characteristics (SPCs) for the other PPIs recommend caution (esomeprazole, pantoprazole),^{28,29} suggest use should be avoided (lansoprazole)³⁰ or contraindicate use (rabeprazole).³¹

What is the treatment of choice for vulvovaginal candidiasis in pregnancy?

Vaginal candidiasis occurs frequently in pregnancy and increases in incidence and severity as the pregnancy progresses.³² Vaginal candidiasis in pregnancy is not associated with adverse outcomes^{33,34} and asymptomatic women do not require treatment.^{33,34}

Topical treatment is preferred to systemic treatment.³³ The **first choice of treatment is with a topical imidazole** (e.g. clotrimazole), either as cream or pessaries;³⁴ there is no evidence that any one imidazole is more effective than another.³⁴ Nystatin cream may also be used.³³ During pregnancy a longer course of treatment may be required for symptom relief.³³ When using pessaries, extra care should be taken to prevent the possibility of mechanical trauma.³⁵

Oral antifungal agents should be avoided in pregnancy due to reports of congenital abnormalities with their use.³³ However a recent review of 800 pregnancy outcomes involving usage of low-dose **fluconazole** ($\leq 150\text{mg}$ daily) suggested a minimal risk of foetal toxicity and suggested that it might be used if considered absolutely necessary in difficult cases.³⁶

How should threadworms be treated during pregnancy?

Threadworm infestation is common in pregnancy.³⁷ **If possible, it should be eradicated by rigorous attention to hygiene.**³⁸ Hygiene measures, which should be continued for 6 weeks involve the following: wearing close fitting underpants at night; showering or bathing each morning while paying particular attention to the perianal area; changing and washing underwear, nightwear and if possible bed linen and towels daily; avoiding the sharing of towels; regular trimming of fingernails; washing hands and scrubbing under the nails first thing in the morning, after using the toilet and changing nappies, and before eating or preparing foods. In addition, toothbrushes should be kept in a closed cupboard and rinsed well before use, and eating in the bedroom should be avoided because of the higher risk of exposure to eggs. **All members of the household should be treated simultaneously.**³⁹

Data on the use of anthelmintic drugs during pregnancy is limited.⁴⁰ **Mebendazole** is the only drug treatment for threadworms currently licensed and available in Ireland, however the SPC lists pregnancy as one of the contraindications to its use.⁴¹ Some specialist pregnancy sources⁴² have suggested mebendazole might be used during pregnancy in helminthic infections that require treatment; however, during the first trimester it should only be used when strictly indicated and when treatment absolutely cannot be delayed. Although in theory, mebendazole, which is poorly absorbed from the gastrointestinal tract, should be unlikely to present a hazard to the human foetus when used during pregnancy, toxicity in animal studies has been noted.^{37,38} If drug treatment is considered absolutely necessary, the available data do not suggest mebendazole causes an overall increased risk of malformations.³⁸

What should be done if a pregnant woman is exposed to chicken pox?

Primary infection with varicella zoster (VZ) can be severe in pregnancy and can threaten foetal and neonatal health.⁴³ Congenital varicella syndrome occurs in 0.4-2.0% of children born to mothers with primary varicella zoster virus infection during the first 20 weeks of gestation. However, cases have been reported as late as the 28th week of gestation.⁴⁴ Pregnant women commonly come into contact with VZ (especially if they already have children) but more than 90% of women are seropositive for VZ antibodies, so contact is not usually a cause for concern. **Seronegative women who have had significant contact with the virus and who do not show clinical signs of chicken pox should be given VZ immunoglobulin (VZIG) as soon as possible and within 96 hours of contact.**⁴⁵ Significant contact has been defined as face-to-face conversation for five minutes, over 15 minutes in the same room, or living in the same household.⁴³ At all stages of pregnancy the primary aim of VZIG immunoprophylaxis is to modify the illness in the mother. **There is little evidence that VZIG will prevent the congenital varicella syndrome following significant exposure of the non-immune mother in the first 20 weeks.**⁴⁵

If a pregnant woman shows clinical signs of chickenpox, she should seek medical advice and avoid contact with other pregnant women and neonates.⁴³ The Royal College of Obstetricians and Gynaecologists has **recommended that aciclovir be given to women with chickenpox if they present within 24 hours of the onset of rash and if they are more than 20 weeks pregnant.**⁴⁶ Although there is a theoretical risk of teratogenesis with use in the first trimester,⁴⁶ no adverse foetal or neonatal effects associated with aciclovir in pregnancy have been reported in a post-marketing pregnancy registry.⁴⁷

Is it safe to use nicotine replacement therapy during pregnancy?

It is well established that smoking during pregnancy can result in miscarriage, premature birth, still-birth and low weight babies.⁴⁸ Clinical studies undertaken in pregnant women who continue to smoke during pregnancy reported that nicotine concentrations in placenta, amniotic fluid and foetal serum, were consistently higher than maternal serum values at various stages during pregnancy.⁴⁹ The foetus is exposed not only to nicotine but also to more than 3,000 harmful chemicals contained in cigarettes.

There is a limited amount of information available on the use of nicotine replacement therapy (NRT) in pregnancy. The foetus is still exposed to nicotine but this should be at a lower level compared with cigarette smoking and without the additional chemicals contained in cigarettes. The UK Committee on the Safety of Medicines (CSM) reviewed the use of NRT during pregnancy and noted that while concerns about the potential adverse effects on the foetus and newborn were often theoretical, the dangers of continuing to smoke were well established and considerably more damaging to both mother and baby.⁴⁸ The Committee recommended that, ideally a pregnant woman should stop smoking without NRT; however, if this was not possible, NRT might be recommended to assist a quit attempt, since the risk of using NRT on the foetus is lower than that expected with smoking. It is recommended that users should be made aware that these therapies should be used as little as possible, and for as short a time as possible in order to aid their

withdrawal.⁴⁹ **The goal of NRT during pregnancy should be to use it as early on in pregnancy as possible with the aim of discontinuing after 2-3 months' use.**

Currently, NRT is available in several formulations in Ireland – gum, lozenge, patch, microtab and inhaler. The SPC for each product recommends using during pregnancy only after advice from a physician and a medical assessment of the benefit/risk ratio.⁵⁰ Only one formulation (Nicotinell® liquorice gum) is contraindicated, due to the presence of liquorice (glycyrrhizin).⁵¹ With regard to the choice of NRT, **it is recommended that the 24-hour patch should not be routinely used, in order to avoid administration of nicotine overnight when the foetus would not normally be exposed to smoking-derived nicotine.**⁴⁸

SUMMARY

Although it is accepted that medicines administered during pregnancy can affect the foetus, up to 80% of pregnant women will take at least one medicine during their pregnancy.⁵² The physiological changes of pregnancy may have an effect on the way a medicine is handled, compared with the non-pregnant state. These include delayed gastric emptying and reduced motility of the small intestine, which may reduce or delay absorption; nausea and vomiting which may also interfere with absorption; increased maternal blood volume and reduced albumin which may alter the expected distribution of a medicine; and changes in medicine-metabolising enzymes and increased renal blood flow which alter the expected rate of clearance of many medicines.⁵³ This, coupled with the fact that medicines are not tested in pregnant women means that available data on safety of use is restricted to observational data collected from actual use in pregnancy. As a result, recommending / prescribing a particular medicine for a pregnant woman may be problematic for the clinician.

Table 2 outlines a possible approach to determining whether the available information justifies the potential risk inherent in the use of a medicine in pregnancy.

Table 2: Questions to ask before prescribing in pregnancy⁵³

- **Is the condition self-limiting / could it be treated by non-pharmacologic means?**
- **If the medicine is not administered what impact might this have on the mother and foetus? (foetal well-being depends on maternal well-being)**
- **What data are available on the medicine? Is there another medicine with a better-known safety profile that could be used instead?**
- **What does the patient understand about the need for this medicine? Concern over a safety risk may result in non-compliance with adverse consequences for mother and foetus**

Ideally, the use of medicines should be avoided during pregnancy, but this is impossible to implement as maternal health is linked to foetal well-being.⁵² It is therefore recommended that a decision to use a specific medicine should be made in consultation with the pregnant woman / woman of reproductive age and a note should be kept on file. In addition, **medicines which have been extensively used in pregnancy and which appear to be usually safe should be prescribed in preference to new or untried medicines, the lowest effective dose should be used and treatment should be stopped as soon as possible.**⁵⁴

Useful Reference Sites for Information on Use of Specific Medicines in Pregnancy

- **British National Formulary (BNF)** is available free on-line (access time limited). It gives a brief outline of recommendations for specific drug classes / individual drugs (Appendix 4)
- **www.medicines.ie** contains the Summaries of Product Characteristics for authorised medicines (particularly brand leaders). Section 4.6 contains the recommendations for use during pregnancy
- **www.imb.ie** contains the Summaries of Product Characteristics for many authorised medicines in Ireland (in Human Medicines / authorised products section). See Section 4.6 as before

References for NMIC Bulletin 2006;12(6): “Frequently Asked Questions on Use of Medicines in Pregnancy (2)”:

1. Le J et al, “Urinary Tract Infections During Pregnancy. *Annals of Pharmacotherapy* 2004; 38: 1692-1701
2. Car J, Urinary tract infections in women: diagnosis and management in primary care. *BMJ* 2006; 332: 94-7
3. Wing D, Pyelonephritis in Pregnancy. *Drugs* 2001; 61(14): 2087-96
4. Management of suspected bacterial urinary tract infection in adults. SIGN guideline No.88 (July 2006). Available at www.sign.ac.uk. Accessed 30th January 2007
5. Urinary tract infection (lower) – women. Prodigy Guidance (July 2006). Available at: www.prodigy.nhs.uk. Accessed 30th January 2007
6. Nicole L et al, Infectious Diseases Society of America Guidelines for the Diagnosis and Treatment of Asymptomatic Bacteriuria in Adults. *Clinical Infectious Diseases* 2005; 40: 643-54
7. Lee A, Inch S, Finnigin D, *Therapeutics in Pregnancy and Lactation*, Publishers: Radcliffe Medical Press, 2000, pages 126-7
8. Delzell J and Lefevre M, Urinary Tract Infections During Pregnancy. *American Family Physician* 2000; 61(3): 713-21
9. Christensen B, Which antibiotics are appropriate for treating bacteriuria in pregnancy? *Journal of Antimicrobial Chemotherapy* 2000; 46 (Suppl. S1): 29-34
10. Schaefer C, *Drugs during pregnancy and lactation: Handbook of prescription drugs and comparative risk assessment*. Publishers Elsevier Science B.V. The Netherlands, 2001. pages 59-63
11. Appendix 4: Pregnancy in British National Formulary (BNF) Number 52. Publishers: BMJ Publishing Group Ltd and RPS Publishing UK, 2006, pages 760-778
12. Briggs G, Freeman R, Yaffe S. *Drugs in Pregnancy and Lactation, Seventh Edition*. Publishers: Lippincott Williams & Wilkins USA. 2005. pages 73,267,340,1153,1632-5
13. National Teratology Information Service (NTIS), Newcastle, monograph on Use of Trimethoprim in Pregnancy (19/12/01). Data on file in NMIC (www.spib.axl.co.uk)
14. Schaefer C, *Drugs during pregnancy and lactation: Handbook of prescription drugs and comparative risk assessment*. Publishers Elsevier Science B.V. The Netherlands, 2001. Chap. 2.1
15. Lee A, Inch S, Finnigin D, *Therapeutics in Pregnancy and Lactation*, Publishers: Radcliffe Medical Press, 2000, pages 23-37
16. Briggs G, Freeman R, Yaffe S. *Drugs in Pregnancy and Lactation, Seventh Edition*. Publishers: Lippincott Williams & Wilkins USA. 2005. pages 7-11
17. Shaheen S et al, Paracetamol use in pregnancy and wheezing in early childhood. *Thorax* 2002; 52:958-3
18. Shaheen S et al, Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. *Clin Exp Allergy* 2005; 35:18-25
19. National Teratology Information Service (NTIS), Newcastle, monograph on Pain Relief During Pregnancy, Jan 2005. Data on file in NMIC (www.spib.axl.co.uk)

20. National Teratology Information Service NTIS), Newcastle, monograph on Use of ibuprofen in pregnancy, Sept 2004. Data on file in NMIC. (www.spib.axl.co.uk)
21. Summary of Product Characteristics for Celebrex®. Available on: www.medicines.ie . Accessed on 13th November 2006
22. Summary of Product Characteristics for Arcoxia®. Available on: www.medicines.ie 30th Accessed on January 2007
23. Micromedex Healthcare Series. Vol.130. Reprotx monograph on codeine. Accessed 13th November 2006
24. Lee A, Inch S, Finnigin D, Therapeutics in Pregnancy and Lactation, Publishers: Radcliffe Medical Press, 2000, pages 49-58
25. Schaefer C, Drugs during pregnancy and lactation: Handbook of prescription drugs and comparative risk assessment. Publishers Elsevier Science B.V. The Netherlands, 2001, pages 149-161
26. The National Teratology Information Service. NHS Northern and Yorkshire Regional Drug and Therapeutics Centre. Proton pump inhibitors in pregnancy. Completed 1/11/01. Data on file in NMIC. (www.spib.axl.co.uk)
27. Nathan A. General care of pregnant women. The Pharmaceutical Journal 2003; 270: 338-340.
28. Summary of Product Characteristics. Nexium®. Astra Zeneca. Accessed online via www.medicines.ie on 6th November 2006
29. Summary of Product Characteristics. Protium®. Atlanta Pharma Ltd. Accessed online via www.medicines.ie on 6th November 2006
30. Summary of Product Characteristics. Zoton®. Wyeth Pharmaceuticals. Accessed online via www.medicines.ie on 6th November 2006
31. Summary of Product Characteristics. Pariet®. Janssen-Cilag Ltd. Accessed online via www.medicines.ie on 6th November 2006
32. The National Teratology Information Service. NHS Northern and Yorkshire Regional Drug and Therapeutics Centre. Monograph on Candidiasis in pregnancy. Data on file in NMIC. (www.spib.axl.co.uk)
33. Ash A, Infections in pregnancy: vaginal infections and STIs, Prescriber 19th March 2005; 16 (6). Available at www.escriber.com
34. Young GL, Jewell D. Topical treatment for vaginal candidiasis (thrush) in pregnancy. Cochrane Database of Systematic Reviews 2001, Issue 4. Art. No.: CD000225. DOI: 10.1002/14651858.CD000225.
35. Summary of Product Characteristics for Canestan®. Available at: www.medicines.ie. Accessed on 24th January 2007
36. Can oral fluconazole be used during pregnancy? UKMi Q&A 147.1. Data on file in NMIC
37. Lee A, Inch S, Finnigin D, Therapeutics in Pregnancy and Lactation, Publishers: Radcliffe Medical Press, 2000, pages 33-34
38. The National Teratology Information Service. NHS Northern and Yorkshire Regional Drug and Therapeutics Centre. Monograph on anthelmintic use in pregnancy, (July 2000). Data on file in NMIC (www.spib.axl.co.uk)
39. Clark C Parasitic worm infestations. PJ 2006;277:343-346
40. Newsholme Q. Diagnosis of management of helminth infections. Prescriber, 5th August 2006; 24-31. Available on www.escriber.com. Accessed on 31st January 2007
41. Summary of Product Characteristics for Vermox®. Available at www.medicines.ie. Accessed 31st January 2007

42. Schaefer C, Drugs during pregnancy and lactation: Handbook of prescription drugs and comparative risk assessment. Publishers Elsevier Science B.V. The Netherlands, 2001, pages 77-78
43. Allen S. Chickenpox and shingles infection. PJ 2006; 277: 453-456
44. Heininger U, Seward J, Varicella. Lancet 2006; 368:1365-1376
45. Immunisation guidelines for Ireland. Draft update (2007). Data on file in NMIC
46. Royal College of Obstetricians and Gynaecologists. Chickenpox in pregnancy (guideline number 13). Available at: www.rcog.org.uk. Accessed 31st January 2007
47. Summary of Product Characteristics for Zovirax® dispersible tablets. Available at: www.medicines.ie. Accessed 31st January 2007
48. Report of the Committee on Safety of Medicines Working Group on Nicotine Replacement Therapy, November 2005. Available at: www.mhra.gov.uk. Accessed on 21st November 2006
49. The National Teratology Information Service. NHS Northern and Yorkshire Regional Drug and Therapeutics Centre. Monograph on Nicotine replacement in pregnancy and nicotine use in pregnancy. Updated version January 2001. Data on file in NMIC. (www.spib.axl.co.uk)
50. Summaries of Product Characteristics for individual NRT products available at www.medicines.ie
51. Summary of Product Characteristics for Nicotinell® liquorice gum. Available online at www.medicines.ie Accessed 21st November 2006
52. Briggs G, Freeman R, Yaffe S. Drugs in Pregnancy and Lactation, Seventh Edition. Publishers: Lippincott Williams & Wilkins USA. 2005. pages xiii-xix
53. Gibson P. Baby Safe: Which drugs are safe during pregnancy? The Canadian Journal of CME 2003; Feb: 67-76
54. McElhatton P, General principles of drug use in pregnancy. PJ 2003. 270: 232-234.