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PRESCRIBING IN PREGNANCY (3): FREQUENTLY ASKED QUESTIONS

- **Infections during pregnancy require adequate treatment to prevent adverse maternal and/or fetal outcomes**
- **Cephalosporins or nitrofurantoin are the currently recommended treatment options for asymptomatic bacteriuria / lower urinary tract infection**
- **Analgesics should be used at the lowest dose for the shortest time; pregnant women should be advised to avoid self-medication with over-the-counter analgesic medicines**
- **Active management of asthma during pregnancy outweighs any potential risks associated with use of asthma medicines**

USE OF ANTIMICROBIAL AGENTS DURING PREGNANCY

A recent study found that antibacterial agents were the second most commonly reported medicine group used during early pregnancy in Ireland.[1] There are few publications evaluating pregnancy outcome following exposure to antibiotics as a group; most publications deal with a specific type of antibiotic or treatment of a specific condition.[2] However, it is important to ensure adequate treatment of maternal infections as failure to treat may lead to adverse maternal and fetal effects as a consequence of uncontrolled infection or fever.[2,3]

Practical Aspects of Prescribing Antimicrobials during Pregnancy

The following general factors need to be considered when managing an infection in a pregnant woman: (1) **maternal factors**, in terms of the nature and severity of infection, (2) **fetal factors**, relating to the potential for harmful outcome due to lack of maternal treatment vs. teratogenic risk with antimicrobial usage, and (3) **the pregnancy state** which is associated with modulation of the immune response and altered pharmacokinetics due to physiological changes.[2,3] Table 1 outlines some general principles for prescribing antimicrobial agents during pregnancy.

Table 1: General principles for antimicrobial prescribing during pregnancy[2-5]

Prior to prescribing	During treatment
Take into account: • The stage of pregnancy • Local antimicrobial sensitivities and resistance data • Prior antimicrobial treatment (for the current and/or previous infections) prescribed during this pregnancy • The allergy status of the pregnant woman • The severity of infection (in terms of impact on maternal status) • Potential for teratogenicity due to exposure of fetus to the proposed antimicrobial agent • Concurrent morbidities / concomitant medications • Microbiological samples should be obtained if possible prior to start of treatment to inform optimum treatment choice	Take into account: • Pharmacokinetic and pharmacodynamic effects of pregnancy on the prescribed antimicrobials – usually need to prescribe at upper end of recommended dosing range • Need to review treatment when culture results become available • If no culture results available, may need to consider empirical treatment switch if no improvement occurs with first antimicrobial agent prescribed

If treatment is required before test results are available, then either **cephalosporins or penicillins** may be used if considered clinically appropriate.[2,6,7] Vital signs should always be checked in women who have any signs or symptoms of possible infection in order to rule out development of sepsis; **if sepsis is suspected, urgent referral to secondary care for intravenous antibiotics is required**.[5,8]

As mentioned in our previous bulletin, the Summary of Product Characteristics is generally regarded as being conservative in relation to its advice on use of medicines in pregnancy. The HSE Clinical Programme in Obstetrics and Gynaecology has published a series of **Antimicrobial Prescribing Guidelines** for the treatment of infections in pregnancy (see **Useful Resources** section at the end of the bulletin).[3-5] The HSE also provides useful information on management of specific infections during pregnancy, including influenza on its website **www.antibioticprescribing.ie**. The following sections discuss frequently asked questions on the use of antibiotics in pregnancy, dealt with by the NMIC clinical enquiry answering service.

Is clarithromycin suitable for use during pregnancy?

Macrolide antibiotics are used in the treatment of many infections due to gram-positive organisms (e.g. infections of the respiratory tract, skin and soft tissues), to gram-negative organisms including *Haemophilus influenzae* and Legionella and to others such as chlamydia and *H Pylori*; they offer an alternative option for patients with penicillin allergy.[9,10] There is a considerable amount of data on their use, as a class, during pregnancy, especially for erythromycin which is the preferred macrolide in some guidelines;[11] however, GI toxicity may limit its use.[9] **Overall, the available evidence does not suggest an increased teratogenic risk for clarithromycin**.[9-12] However, several studies have suggested a **potential increased risk for miscarriage when clarithromycin is used in the first trimester**; a recent nationwide cohort study in Denmark (n>900,000 pregnancies) noted an increased hazard of miscarriage with the use of clarithromycin (but not with use of erythromycin or penicillin) in the first trimester of pregnancy.[13] However, this association may be due to confounding by indication (i.e. due to underlying infection). Current guidance states that clarithromycin may be used in pregnancy when the resistance spectrum requires it or in the presence of penicillin allergy.[9,12]

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

Urinary tract infection (UTI) in pregnancy is the most common non-obstetric reason for admission to hospital during pregnancy.[14,15] UTIs can cause morbidity including preterm labour, and sepsis. Lower UTI occurs in approximately 1 to 4% of pregnancies; it may present as asymptomatic bacteriuria (ASB) or as cystitis.[14] If either is identified, prompt

treatment with antibiotics (usually for at least 7 days) is required to prevent progression to acute pyelonephritis (seen in 0.5 to 2% of pregnant women).[14,16] Typical causative organisms are gram-negative organisms such as *E. Coli*, followed by Group B streptococcus or enterococcus.[3,14] **Cephalosporins or nitrofurantoin are recommended as the optimal treatment options for asymptomatic bacteriuria / lower UTI**; *E. Coli* may be resistant to **amoxicillin** / **co-amoxiclav**; therefore these penicillins should only be used if the organism is known to be susceptible (7 day treatment course).[3,17,18]
Cephalosporins: The majority of the available data on their use during pregnancy do not suggest that therapeutic dosages are associated with either any congenital malformation or an increased risk of miscarriage.[7] Therefore cephalosporins may be used at any stage of pregnancy, if clinically indicated. **The national guidelines recommend cefalexin at a dose of 500mg twice to three times daily for 7 days**.[3,17]
Nitrofurantoin has been used during pregnancy for many years;[19] it is particularly useful in the presence of penicillin allergy.[4] The available published data does not establish an increased risk of malformations or neonatal problems following exposure during pregnancy.[4,19] **Use should be avoided near term** (> 36 weeks) due to the risk of haemolytic anaemia; haemolysis has been noted with its use in non-pregnant patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and haemolytic anaemia has also been observed when nitrofurantoin was used shortly before delivery.[4,16,19,20] **The national guidelines recommend nitrofurantoin at a dose of 50 to 100mg four times daily for 7 days**.[3,17]
Quinolones should be generally avoided during pregnancy, because of the theoretical risk of arthropathy (based on juvenile animal study findings);[2,4] however no adverse effects have been noted with the use of ciprofloxacin during pregnancy to date.[4,21] If required, **ciprofloxacin may be used as a second-line option** e.g. to treat a resistant strain of infection, not amenable to first-line therapy.[2,4]
Trimethoprim is an anti-folate agent and most guidelines recommend that **use should be avoided during pregnancy particularly in the first trimester**, because of theoretical concerns that it may limit the availability of folic acid to the fetus, which is required for normal development.[2,16] If usage is warranted during pregnancy a detailed benefit/risk assessment should be carried out and the patient should receive adequate folate supplementation (specialist supervision recommended).[2,4]

Practice points for managing urinary tract infection (UTI) in primary care

- A urine sample should normally be sent for analysis prior to initiating antibiotic therapy and should be repeated following completion of antibiotic treatment to confirm clearance of the organism
- Cefalexin or nitrofurantoin therapy for 7 days is the recommended empirical first-choice antibiotic therapy for lower UTI in a pregnant woman
- If the patient has signs of sepsis or systemic illness, she should be referred urgently to secondary care for intravenous antibiotics
- Patients with recurrent confirmed UTIs should be referred to secondary care for further investigations

How should threadworms be treated during pregnancy?

Threadworm/pinworm infestation (enterobiasis) is not usually considered a serious threat to health; therefore it is recommended that where possible **infestation in pregnancy should be eradicated by rigorous attention to hygiene for at least six weeks**.[22] Information is available on appropriate hygiene methods at: **www.hse.ie/eng/health/az/e/enterobiasis/**. If drug treatment is considered necessary, due to overwhelming infestation, **mebendazole** may be considered; however, **it should be delayed until after the first trimester if possible** as there are limited data relating to its use in the first trimester.[9,23] Data from usage in second and third trimesters have suggested no increased risk of fetal toxicity.[23,24] [Note: the authorised mebendazole preparation states that use is contra-indicated during pregnancy][25]

PAIN RELIEF IN PREGNANCY

There are no specific guidelines for the management of pain during pregnancy.[26] Severe or chronic pain, if left untreated may have adverse effects on the mother and fetus. If **non-pharmacological methods of alleviating pain** (such as heat, ice, massage or physiotherapy) are not successful, then pharmacotherapy may be required.[26,27] Table 2 summarises known safety data for the most commonly used analgesic agents during pregnancy. **Pregnant women should be advised not to take over-the-counter remedies** (which may contain analgesics either alone or in compound preparations) without physician or pharmacist advice.[26,28]

Table 2: Analgesic options during pregnancy [26,28-40]

Drug name / class	Safety of use during pregnancy
Paracetamol	Can be used during all stages of pregnancy for mild to moderate pain or pyrexia (max recommended dose 4g/day). Conflicting results on risk of wheeze in infants with regular use in pregnancy after 20 weeks.
NSAIDs (incl. aspirin)	Conflicting data in relation to increased risk of miscarriage and malformations (cardiovascular defects and/or oral clefts); therefore, need to assess potential benefits vs. risks of use during first and second trimester before use. NSAID use after 30 weeks' gestation is associated with increased risk of premature closure of the ductus arteriosus, oligohydramnios, neonatal bleeding and potentially PPH (due to inhibitory effects on PGs). Preferred agent is ibuprofen as most data are available on its use. Selective COX-2 inhibitors should not be used due to lack of experience of use and potential effects on fetal kidneys.
Opioids	Potential teratogenic risks are poorly defined due to conflicting study results. Most data available for codeine (less data for morphine). Class effects include: theoretical risk of respiratory depression in neonate if used nearer term; risk of NAS if used chronically / near time of delivery (risk > for morphine than for codeine). There is a lack of information on clinical safety of use of oxycodone, fentanyl or tramadol during pregnancy, therefore their use is not usually recommended.

NSAID=non-steroidal anti-inflammatory drug; PPH=persistent pulmonary hypertension; PG=prostaglandin; NAS=neonatal adaptation syndrome

Practical Aspects of Prescribing Analgesia during Pregnancy

In general, when required, **analgesics should be used at the lowest effective dose for the shortest time period during pregnancy**.[26] If **NSAIDs** are required for pain relief a benefit/risk assessment of such treatment should be undertaken prior to use (see table 2); in view of the toxicity concerns for the offspring reported with their use during the third trimester, NSAIDs should only be prescribed under specialist supervision, to ensure that fetal wellbeing is monitored appropriately.[31-34] [See also the section on *Hypertension in Pregnancy* in the bulletin: Prescribing in Pregnancy (2) for information on the use of **low dose aspirin** during pregnancy]
Opioid analgesics have been used for the **short-term management of pain** during pregnancy not controlled by

other medicines. **Conflicting results in relation to codeine use in pregnancy and certain heart defects have been found**; limited information is available for other opioid agents.[35-40] Chronic usage or use in third trimester near to term, is associated with neonatal complications (Table 2). [Note: **codeine use is contraindicated during breastfeeding**][36]

Neuropathic pain: For many of the medicines recommended by NICE for the management of neuropathic pain (e.g. **gabapentin**, **pregabalin, duloxetine**), no conclusion regarding risk during pregnancy can be provided, due to lack of human data; animal data suggest risk to the fetus.[26,41-44] Therefore their use is only recommended if the benefits are deemed to outweigh the potential risks to the fetus. **Carbamazepine and other anti-convulsants are not recommended for neuropathic pain**; usage has been associated with increased risk of congenital malformations due to prenatal exposure.[26,41][See migraine section for information on amitriptyline]

How should migraine be managed during pregnancy?

Migraine is one of the most common neurological complaints in pregnancy.[45] Many women with pre-existing migraine may see improvement especially during the second and third trimesters; however migraine with aura often has an unpredictable course and migraine may present for the first time during pregnancy in some women.[45,46] **It is important to rule out secondary causes for first time presentation of migraine-type headache** (including hypertension or pre-eclampsia, more rarely subarachnoid haemorrhage, meningitis or space-occupying lesions).[46,47]

Non-pharmacological management strategies should be tried before therapy is considered; these include identification (and avoidance) of trigger factors, adequate hydration (minimum of 2 litres/day), regular meals, reduction of caffeine intake (which should be done slowly to avoid rebound headache), sleep hygiene, regular exercise, and relaxation therapy / biofeedback if available.[45-48]

Pharmacotherapy: Based on its well-defined benefit/risk profile during pregnancy, **paracetamol** is the first-line choice for migraine; however, it may not relieve severe migraine.[45,46] Second-line options include **triptans**[46-48] or NSAIDs (see Table 2). The majority of safety data on use of triptans during pregnancy relates to **sumatriptan**; evidence from pregnancy registries and other studies suggest that it is a safe therapeutic option for use throughout pregnancy.[48,49] Therefore this is the recommended triptan for use during pregnancy.[49] If a woman has been taking **an alternative triptan** prior to conception, an individual risk / benefit analysis of continuing that therapy versus switching to sumatriptan needs to be made and discussed with the pregnant woman.[49] Opioids may exacerbate migraine-related GI symptoms and chronic use may increase the risk of medication overuse headache.[45]

Antiemetic therapies may also be needed for the management of migraine-associated nausea and vomiting; **first-line options** include prochlorperazine and cyclizine.[45] [See also section on *Antiemetic Therapy in Pregnancy* in the bulletin: Prescribing in Pregnancy (2)]

Prophylactic therapy should be considered only if migraine attacks occur more than once a week or if the attacks are causing significant disability; specialist advice is recommended.[47,50] **Low dose aspirin** (75mg/d) may be helpful; several clinical trials, evaluating its use in pre-eclampsia have shown that aspirin (up to 150mg/d) is safe to use up to at least 36 weeks' gestation.[34,51] **Beta-blockers** are recommended as first-line for migraine prophylaxis in the non-pregnant setting (e.g. propranolol).[50] Available data suggest that low dose propranolol is safe to use during first and second trimesters of pregnancy; some experts recommend that it should be discontinued in the third trimester to reduce the risk of fetal bradycardia.[47] The **tricyclic antidepressant** (TCA) **amitriptyline** (10 to 35mg at night) may also be considered.[45,46] There is an increased likelihood of withdrawal symptoms in the neonate and/or poor neonatal adaptation syndrome if TCAs are used throughout pregnancy or near delivery.[52,53] The anti-convulsant **topiramate should not be used for migraine prophylaxis due to the risk of teratogenicity**.[34,47]

Can all asthma medicines be used during pregnancy?

Asthma affects 4 to 12% of pregnant women worldwide.[54] Asthma control often changes during pregnancy; in about one-third of women asthma symptoms worsen, in one-third they improve and in the one-third there is no change.[55] Exacerbations are common, especially in the second trimester, and pregnant women are particularly susceptible to the effects of viral respiratory infections (e.g. influenza).

Active management of asthma during pregnancy has been shown to outweigh any potential risks associated with normal usage of reliever and controller medications, not only in terms of the wellbeing of the woman but also in ensuring proper fetal oxygenation and normal growth.[55,56] The 2018 update of the **GINA global strategy for asthma management and prevention for adults recommends that the standard stepped approach to asthma care outlined for non-pregnant adults should also be followed during pregnancy**. Table 4 summarises the commonly used anti-asthmatic preparations with their currently available pregnancy-related safety information and advice on use during pregnancy.

Table 4: Anti-asthmatic medications that may be used during pregnancy [54-61]

Drug class	Pregnancy safety data	Advice on use in pregnancy
Beta$_2$-agonists -short-acting (SABA) -long-acting (LABA)	No evidence of fetal harm; extensive data available for SABA (as on-demand reliever medication); moderate data available for LABA (as chronic use in association with ICS)	Salbutamol or terbutaline (first-line SABA); salmeterol or formoterol (first-line LABA)
Inhaled corticosteroids (ICS)	No evidence of fetal harm; most evidence for budesonide / beclometasone but no suggestion of harm with other ICS	First-line option for long-term management in pregnancy
Theophylline	No evidence of embryotoxicity but should be used at the lowest effective dose (risk of producing tremor, vomiting and tachycardia in the pregnant woman, and possibly the fetus in utero)	Recommended use is as add-on option when ICS / beta$_2$-agonist combination fails to control symptoms
Leukotriene receptor antagonists (LTRA) -montelukast -zafirlukast	Limited and conflicting safety data reported with use; additional fetal monitoring recommended if used during the first trimester	Recommended use is as add-on option when ICS / beta$_2$-agonist combination fails to control symptoms
Oral corticosteroids (CS) (specialist supervision)	Large epidemiologic studies suggest a risk of ↓ in birth weight, a small ↑in the incidence of cleft lip (+/- cleft palate) and potential risk of cataracts in offspring (uncertain causality)	Impact of stopping oral CS on mother's health vs. potential adverse fetal outcome to be assessed on an individual basis
Monoclonal antibodies -anti-IgE / anti-IL-5 (specialist supervision)	Limited data on use of these agents during pregnancy	To be used only if benefit outweighs potential risk to fetus

If a pregnant woman requires more than just reliever medication with short-acting inhaled beta$_2$-agonists on an "as required" basis, then **inhaled corticosteroids** (ICS) **are the treatment of choice for long-term asthma management throughout pregnancy**.[55] They should not be withheld or stopped at any stage.[58,59] ICS have been shown to reduce exacerbations; moreover, there is strong evidence showing that **cessation of ICS during pregnancy is a significant risk factor for exacerbation**.[55] An individual benefit / risk assessment should be made for each "add-on" or specialist medicine used for patients with severe or allergic asthma (see Table 4).[58]

Adherence to asthma therapy. Although all guidelines recommend continuation of asthma medication during pregnancy, some women may choose to discontinue or reduce their asthma medication for fear of causing harm to the fetus.[60] The Asthma Society of Ireland has produced a patient guide on "Asthma and Pregnancy" (**www.asthma.ie/document-bank/pregnancy-booklet-final-2**). This provides helpful general and pharmacologic advice on managing asthma during pregnancy and includes a simple **5-step rule** to follow in the case of an **asthma attack**.

What is the advice on use of topical corticosteroids in pregnancy?

Many patients with psoriasis experience remission or improvement in symptoms during pregnancy, thought to be due to the immunologic changes occurring during pregnancy.[62] However **atopic eczema (also known as atopic eruption of pregnancy, AEP) is a recognised specific dermatosis of pregnancy**.[63] Only 20% of patients who develop AEP have a pre-pregnancy history of atopic eczema and the condition tends to occur during the first and second trimesters.[62] **If topical corticosteroids (CS) are required at any stage of pregnancy, treatment should not be withheld**.[64] The majority of data relating to topical CS do not indicate that use in early pregnancy increases the risk of orofacial clefts in the offspring (unlike oral CS). Data from a UK cohort study suggested a 3% increase in relative risk for fetal growth restriction with use of each additional 30g tube (= normal size) of any potent or very potent topical CS prescribed during pregnancy.[65] A recent guideline has recommended use of mild / moderately potent topical CS as first-line treatment if topical CS are needed during pregnancy (e.g. hydrocortisone 1% or clobetasone butyrate 0.05%).[63] Potent or very potent topical CS should be used as second-line therapy; they should be used for the shortest duration possible in view of the potential for fetal growth restriction. [See the **Useful Resources** section for information on availability of patient leaflets on AEP]

Is there evidence to support the use of biologicals in pregnancy?

Biological agents play an important role in the management of many immune-related diseases (e.g. rheumatoid arthritis, inflammatory bowel disease, psoriasis).[66] For most of these diseases, if conception occurs at a time of quiescent disease, the level of disease activity during pregnancy remains low and similar to that in non-pregnant women, with no adverse outcome on the fetus.[67,68] Biological agents (e.g. TNF-alpha inhibitors and anti-interleukin antibodies) are usually prescribed only when prior immunomodulatory therapies have not worked or were not tolerated.[66] These agents are used under the supervision of multidisciplinary specialist-led teams, which includes patient education and involvement in the optimum management of their disease, including advice regarding conception.[68,70] **If a patient on biological therapy has an unintended pregnancy, she should be advised to seek advice immediately from her specialist team on whether to continue / discontinue these agents**. Patient leaflets on the individual agents are available to download from **www.medicinesinpregnancy.org/**, which may help to explain the benefit/risk of each treatment.

If biological agents are deemed necessary to control disease activity, many guidelines recommend their continued use during pregnancy.[67-70] While some biological agents appear to have a low rate of placental transfer, some of the anti-TNF-alpha agents (e.g. infliximab, adalimumab) have been shown to cross the placenta after 20 weeks, which may potentially interfere with the development of the fetal immune system.[66,71-73] The National Immunisation Advisory Committee recommends that administration of **rotavirus vaccine should be deferred until 4 and 6 months of age** in an infant of a woman who has been treated with an immunomodulator during pregnancy, if immunosuppression (due to the maternal biological disease modifying agent) is anticipated to be moderate or severe.[74] If in doubt, it is recommended that the supervising specialist team should be consulted. **BCG is also contraindicated** in the first 6 months of age in this setting. [See *Immunisation Guidelines for Ireland*, Chapter 3, update July 2018]

USEFUL RESOURCES

- The HSE Clinical programme in Obstetrics and Gynaecology has produced clinical guidelines on treatment regimens of pregnancy-related infections, with safety information on individual antimicrobial agents: **www.hse.ie/eng/about/who/cspd/ncps/obstetrics-gynaecology/resources/national-clinical-guidelines/**
- The HSE antibiotic prescribing website provides useful information on management of various infections, including influenza, during pregnancy, for primary care: **www.antibioticprescribing.ie**
- The 2018 update on global strategy for asthma management and prevention for adults (GINA) is available at: **https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention**
- The UK Teratology information service, provides individual safety monographs for medicines: **www.uktis.org/** (the abstracts are free, subscription is required for full monographs)
- Best Use of Medicines in Pregnancy (BUMPs) provides information leaflets for pregnant women and their partners, which are freely available at: **www.medicinesinpregnancy.org/**
- The European Association of Dermatology & Venereology has developed useful patient leaflets on skin conditions in pregnancy and on the various drug treatments: **www.eadv.org/patient-corner/leaflets/**
- The Summary of Product Characteristics for individual medicines is available at: **www.hpra.ie** / **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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References for Pregnancy bulletin

1. Cleary B et al, Medication use in early pregnancy – prevalence and determinants of use in a prospective cohort of women. Pharmacoepi and Drug Safety 2010; 19: 408-17

2. Antibiotic use in pregnancy, February 2013 Version 1.0. UK Teratology Information Service (ukTiS). Available online at: www.toxbase.org/Poisons-Index-A-Z/A-Products/Antibiotic-use-in-Pregnancy/. Accessed 18th April 2018.

3. Medication Guidelines for Obstetrics and Gynaecology. First Edition, Volume 1: Antimicrobial Prescribing Guidelines (January 2017/amended Sept 2017). Available online at: www.hse.ie/eng/about/who/cspd/ncps/obstetrics-gynaecology/resources/national-clinical-guidelines. Accessed 19th June 2018.

4. Medication Guidelines for Obstetrics and Gynaecology. First Edition, Volume 2: Antimicrobial safety in pregnancy and lactation. November 2016. Available online at: www.hse.ie/eng/about/who/cspd/ncps/obstetrics-gynaecology/resources/national-clinical-guidelines/. Accessed 19th June 2018.

5. Clinical Practice Guideline: bacterial infections specific to pregnancy. Institute of obstetricians and gynaecologists, RCPI and the National Programme in Obstetrics and gynaecology. Version 1.0. February 2015. Available online at: www.hse.ie/eng/about/who/cspd/ncps/obstetrics-gynaecology/resources/national-clinical-guidelines. Accessed 19th June 2018

6. Penicillin antibiotics in pregnancy (Date of issue: June 2017) UK Teratology Information Service (ukTiS). Available online at: https://www.toxbase.org/Poisons-Index-A-Z/P-Products/Penicillin-antibiotics-in-pregnancy/. Accessed 15th June 2018

7. Use of cephalosporins in pregnancy (June 2017). UK Teratology Information Service (ukTiS). Available online at: http://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-CEPHALOSPORINS-IN-PREGNANCY/. Accessed 15th June 2018

8. Knight M, et al, Messages for the prevention and treatment of sepsis in Saving Lives, Improving Mothers' Care: Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2013–15. MBRRACE-UK December 2017 (pages 59-69). Available online at: www.npeu.ox.ac.uk/mbrrace-uk/reports. Accessed 3rd July 2018

9. Padberg S, Anti-infective agents, in Drugs during Pregnancy and Lactation: treatment options and risk assessment (Third Edition). Christof Schaefer, Paul Peters, and Richard K. Miller (Editors). Elsevier B.V. UK. 2015. Chapter 2.6 pps 116-177

10. Klacid® Summary of Product Characteristics. Available online at: www.medicines.ie. Accessed 27th June 2018

11. Macrolides in pregnancy. (Date of issue: June 2017, Version: 2.1). UK Teratology Information Service (ukTiS). Available online at: www.toxbase.org/Poisons-Index-A-Z/M-Products/Macrolides-in-pregnancy/. Accessed 27 June 2018

12. Clarithromycin in Drugs in Pregnancy and Lactation. Briggs (11th Edition). Available online via MedicinesComplete database. Accessed 27 June 2018

13. Andersen JT et al, Clarithromycin in Early Pregnancy and the Risk of Miscarriage and Malformation: A Register Based Nationwide Cohort Study PLOS ONE 8(1): e53327. https://doi.org/10.1371/journal.pone.0053327. Accessed 27 June 2018

14. Johnston C et al, [10-MINUTE CONSULTATION] A likely urinary tract infection in a pregnant woman. BMJ 2017;357:j1777 doi: 10.1136/bmj.j1777 (Published 2017 April 27)

15. Clinical Practice guideline. Management of UTI in pregnancy. Institute of Obstetrics and Gynaecology. Royal College of Physicians in Ireland. Version 1.0 2015. Available online at: www.rcpi.ie. Accessed 4th April 2018

16. Urinary Tract Infections. BNF online. Available at: https://doi.org/10.18578/BNF.256452653. Accessed 15th June 2018

17. UTI in pregnancy. [HSE Antibiotic Prescribing website]. Available online at: www.hse.ie/eng/services/list/2/gp/antibiotic-prescribing/conditions-and-treatments/urinary/uti-in-pregnancy/. Accessed 19 June 2018.

18. Augmentin® Summary of Product Characteristics. Available online at: www.medicines.ie. Accessed 27th June 2018.

19. Nitrofurantoin in pregnancy (June 2017). UK Teratology Information Service (ukTiS). Available online at: https://www.toxbase.org/Poisons-Index-A-Z/N-Products/Nitrofurantoin-in-pregnancy/. Accessed 15th June 2018

20. Nitrofurantoin patient leaflet. Available from BUMPS (best use of medicines in pregnancy). UK Teratology Information Service (ukTiS). Available online at: http://www.medicinesinpregnancy.org/Medicine--pregnancy/. Accessed 15th June 2018

21. Ciproxin 750mg Film-coated Tablets® Summary of Product Characteristics. Available online at: www.medicines.ie. Accessed 6th July 2018

22. TREATMENT OF THREADWORM/PINWORM IN PREGNANCY (Date of issue: January 2018, Version: 2). UK Teratology Information Service (ukTiS). Available online at: www.toxbase.org/Bumps/Mongoraph-Data/USE-OF-ANTHELMINTICS-IN-PREGNANCY/. Accessed 27th June 2018

23. Mebendazole in Pregnancy (Date of issue: January 2014, Version: 3), UK Teratology Information Service (ukTiS). Available online at: www.toxbase.org/Poisons-Index-A-Z/M-Products/Mebendazole-in-Pregnancy/. Accessed 27th June 2018

24. Mebendazole *in* Drugs in Pregnancy and Lactation. Briggs (11th Edition). Available online via MedicinesComplete database. Accessed 27th June 2018

25. Vermox® Summary of Product Characteristics. Available online at: www.medicines.ie. Accessed 27th June 2018

26. Pain relief in pregnancy, August 2016 Version 2.1. UK Teratology Information Service (UKtis). Available online at: www.toxbase.org/Poisons-Index-A-Z/P-Products/Pain-relief-in-pregnancy/. Accessed 18th April 2018

27. Non-pharmacological Pain Management Therapies for Adults (February 28, 2018). Available online at: www.drugs.com/cg/non-pharmacological-pain-management-therapies-for-adults. Accessed 5th July 2018

28. Anca B et al, over the counter drugs during pregnancy – tips for a correct approach. Therapeutics, Pharmacology and Clinical Toxicology 2014; Vol XVIII: 116-120

29. Chambers C, over-the-counter medications: risk and safety in pregnancy. Seminars in Perinatology 2015; 39: 541-4

30. Paracetamol in pregnancy. UK Teratology Information Service (ukTiS). Available online at: www.toxbase.org/Poisons-Index-A-Z/P-Products/Paracetamol-Therapeutic-Use-in-Pregnancy/. Accessed 20 June 2018

31. Use of NSAIDs in pregnancy. UK Teratology Information Service (ukTiS). Available online at: https://www.toxbase.org/Bumps/Mongoraph-Data/USE-OF-NON-STEROIDAL-ANTI-INFLAMMATORY-DRUGS-NSAIDs-IN-PREGNANCY/. Accessed 15th June 2018

32. Ibuprofen in pregnancy, December 2013, Version 1.1. UK Teratology Information Service (ukTiS). Available online at: www.toxbase.org/Poisons-Index-A-Z/I-Products/Ibuprofen-in-Pregnancy/. Accessed 15th June 2018

33. IBUPROFEN on “Reprotox”. Available via Micromedex database. Accessed 13th August 2018

34. Malm H and Borisch C, Analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) muscle relaxants, and antigout medications, *in* Drugs during Pregnancy and Lactation: treatment options and risk assessment (Third Edition). Christof Schaefer, Paul Peters, and Richard K. Miller (Editors). Elsevier B.V. UK. 2015. Chapter 2.1 pps 27-58.

35. Morphine in pregnancy. ukTiS. Available online at: www.toxbase.org/Poisons-Index-A-Z/M-Products/Morphine-in-pregnancy/. Accessed 20 June 2018

36. Codeine in pregnancy. ukTiS. Available online at: www.toxbase.org/Bumps/Mongoraph-Data/USE-OF-CODEINE-IN-PREGNANCY/. Accessed 20 June 2018

37. Tramadol in pregnancy. UK Teratology Information Service (ukTiS). Available online at: www.toxbase.org/Poisons-Index-A-Z/T-Products/Tramadol-in-pregnancy/. Accessed 20 June 2018

38. Durogesic® Summary of Product Characteristics. Available online at: www.medicines.ie. Accessed 22 June 2018

39. Zydol® Summary of Product Characteristics. Available online at: www.medicines.ie. Accessed 22 June 2018

40. /Oxynorm® Summary of Product Characteristics. Available online at: www.medicines.ie. Accessed 22 June 2018

41. Chambers C and Schaefer, Epilepsy and antiepileptic medications, *in* Drugs during Pregnancy and Lactation: treatment options and risk assessment (Third Edition). Christof Schaefer, Paul Peters, and Richard K. Miller (Editors). Elsevier B.V. UK. 2015. Chapter 2.10 pps 252-293

42. Neuropathic pain in adults: pharmacological management in non-specialist settings. National Institute of Health and Care Excellence (20 November 2013). Available online at: www.nice.org.uk/guidance/cg173. Accessed 22 June 2018

43. Pregabalin *in* Drugs in Pregnancy and Lactation. Briggs (11th Edition). Available online via MedicinesComplete database. Accessed 3rd July 2018

44. Pregabalin *in* AHFS Drug Information. Available online via MedicinesComplete database. Accessed 3rd July 2018

45. Jarvis S et al, Managing migraine in pregnancy: 10-minute consultation. BMJ 2018; 360: k80

46. Migraine in pregnancy, August 2016 Version 2.1. UK Teratology Information Service (ukTiS). Available online at: https://www.toxbase.org/Bumps/Monogaph-Data/TREATMENT-OF-MIGRAINE-IN-PREGNANCY/. Accessed 15th June 2018

47. Hammond N, A 25-year old pregnant woman with worsening headaches. Medscape 7th June 2018. Available online at: https://reference.medscape.com/viewarticle/897549/ Accessed 20th June 2018

48. Duong S et al, Safety of triptans for migraine headaches during pregnancy and breastfeeding. Canadian Family Physician 2010; 56: 537-539

49. Triptans in pregnancy, October 2015 Version 1. UK Teratology Information Service (ukTiS). Available online at: www.toxbase.org/Poisons-Index/A-Z/T-Products/Triptans-in-pregnancy/. Accessed 15th June 2018

50. Headaches in over 12s: diagnosis and management. NICE Clinical guideline. Published 19 September 2012. Available online at: www.nice.org.uk/guidance/cg150. Accessed 23rd June 2018

51. Rolnik DL, Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. N Engl J Med 2017;377:613-22

52. Tricyclic antidepressants in pregnancy February 2018, Version: 2. UK Teratology Information Service (ukTiS). Available online at: www.toxbase.org/Poisons-Index-A-Z/T-Products/Tricyclic-antidepressants-in-pregnancy/. Accessed 25th June 2018

53. Amitriptyline 25mg tablets® Summary of Product Characteristics. Available online at: www.hpra.ie. Accessed 25th June 2018

54. Goldstein L et al, Antiasthmatic and cough medication, *in* Drugs during Pregnancy and Lactation: treatment options and risk assessment (Third Edition). Christof Schaefer, Paul

Peters, and Richard K. Miller (Editors). Elsevier B.V. UK. 2015. Chapter 2.3 pp 66-74 2018

55. GINA Report, Global Strategy for Asthma Management and Prevention. Available online at: https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed 26 June 2018

56. Charlton R et al, Asthma medication prescribing before, during and after pregnancy: a study in seven European regions. BMJ Open 2016; 6:e009237.doi:10.1136/bmjopen-2015;009237

57. Beclometasone / budesonide *in* Drugs in Pregnancy and Lactation. Briggs (11th Edition). Available online via MedicinesComplete database. Accessed 26th June 2018

58. Goldstein L et al, antiasthmatic and cough medication, *in* Drugs during Pregnancy and Lactation: treatment options and risk assessment (Third Edition). Christof Schaefer, Paul Peters, and Richard K. Miller (Editors). Elsevier B.V. UK. 2015. Chapter 2.3 pps 266-74

59. Inhaled corticosteroids in pregnancy December 2016, Version: 1.1. UK Teratology Information Service (ukTiS). Available online at: www.toxbase.org/Poisons-Index-A-Z/I-Products/Inhaled-corticosteroids-in-pregnancy/. Accessed 26th June 2018

60. Lim A et al, Systematic Review of the Safety of Regular Preventive Asthma Medications during Pregnancy. Ann Pharmacother 2011 ;45:931-45

61. Montelukast in pregnancy, August 2015, Version: 2.1. UK Teratology Information Service (ukTiS). Available online at: www.toxbase.org/Poisons-Index-A-Z/M-Products/Montelukast-in-pregnancy/. Accessed 26th June 2018

62. Ambros-Rudolph C et al, The specific dermatoses of pregnancy revisited and reclassified: Results of a retrospective two-centre study on 505 pregnant patients. J AM ACAD DERMATOL 2006; 54: 395-404

63. Chi CC et al, Evidence-based (S3) guideline on topical corticosteroids in pregnancy. Brit J Dermatol 2011; 165: 943-52

64. Topical corticosteroids in pregnancy, December 2016, Version: 1. UK Teratology Information Service (ukTiS). Available online at: www.toxbase.org/Poisons-Index-A-Z/T-Products/Topical-corticosteroids-in-pregnancy/. Accessed 2nd July 2018

65. Chi CC et al, Safety of topical corticosteroids in pregnancy: a population-based cohort study. J Invest. Dermatol 2011; 131: 884-91

66. Weber-Schondorfer C, Immunosuppression, rheumatic diseases, multiple sclerosis, and Wilson's disease *in* Drugs during Pregnancy and Lactation: treatment options and risk assessment (Third Edition). Christof Schaefer, Paul Peters, and Richard K. Miller (Editors). Elsevier B.V. UK. 2015. Chapter 2.12 pps 341-373

67. Van den Brandt S et al, Risk factors for flare and treatment of disease flares during pregnancy in rheumatoid arthritis and axial spondyloarthritis patients. Arthritis Research & Therapy 2017; 19:64-73

68. Van der Woude CJ et al, The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. J Crohns Colitis 2015; 107-124. Doi: 10.1093/ecco-jcc/jju006

69. Mahadevan U et al, The London position statement of the World Congress of Gastroenterology on biological therapy for IBD with the European Crohn's and Colitis Organization: pregnancy and pediatrics. Am J Gastroenterol 2011; 106: 214–23.

70. Skorpen C et al, The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann. Rheum Dis 2016; 75: 795-810

71. Adalimumab in Pregnancy: May 2015, Version: 2. UK Teratology Information Service (ukTiS). Available online at: www.toxbase.org/Poisons-Index-A-Z/A-Products/Adalimumab-in-Pregnancy/. Accessed 4th July 2018

72. Etanercept in pregnancy: July 2015, Version: 2. UK Teratology Information Service (ukTiS). Available online at: www.toxbase.org/Poisons-Index-A-Z/E-Products/Etanercept-in-pregnancy/. Accessed 4th July 2018

73. Infliximab in pregnancy: July 2015, Version: 2. UK Teratology Information Service (ukTiS). Available online at: www.toxbase.org/Poisons-Index-A-Z/I-Products/Infliximab-in-pregnancy/. Accessed 14th August 2018

74. Update on rotavirus guidance (19th July 2018) National Immunisation guidelines for Ireland (Chapter 3). Available at: www.hse.ie/eng/health/immunisation/hcpinfo/othervaccines/rotavirus/. Accessed 13th August 2018