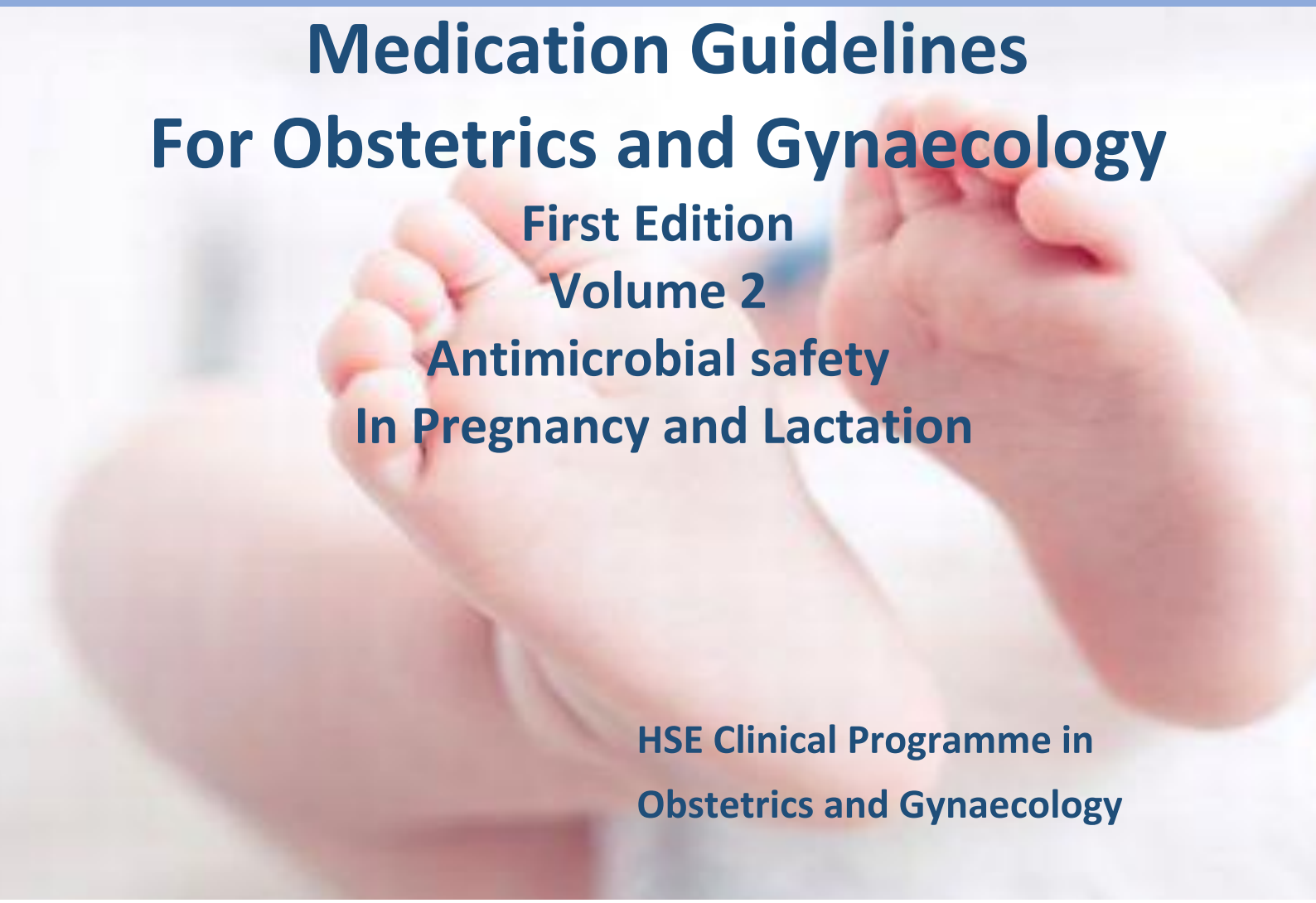
Medication Guidelines For Obstetrics and Gynaecology

First Edition

Volume 2

Antimicrobial safety In Pregnancy and Lactation



HSE Clinical Programme in Obstetrics and Gynaecology

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OBSTETRICS AND GYNAECOLOGY

Preface

The purpose of this First Edition of National Medications Programme (Volume 2) of Antimicrobial Safety in Pregnancy and Breastfeeding is as a sister document to the Antimicrobial Prescribing Guidelines in Obstetrics. This document provides the current safety data on antimicrobial use in pregnancy and lactation and is to be used as a guide to prescribers when choosing appropriate antimicrobial treatment for the pregnant woman. The National Medications Programme in Obstetrics aim is to improve the quality of care for all women and their offspring attending our maternity services whatever the setting. It follows the development of a number of clinical practice guidelines for infections and pregnancy by the Clinical Programme in Obstetrics and Gynaecology. It addresses one of the key priorities identified by the National Implementation Group which supports the implementation of the HIQA Patient Safety Investigation report into services at University Hospital Galway.

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1.1 Safety in pregnancy – an overview

In general, agents cannot be classified as teratogens or nonteratogens without consideration of the dose, route, duration and gestational timing of the treatment (1). Congenital defect can be defined as an anatomical anomaly but may also be a metabolic or functional (including mental retardation) anomaly caused by a genetic alteration or a physical, chemical or infectious agent reacting during prenatal life (2).

The greatest teratogenic risk is 3 to 8 weeks after conception (5 to 10 weeks gestation) (3). Stopping a drug after week 10, due to concerns about Teratogenesis, does not usually reduce the risk substantially (3). Fetotoxicity refers to the functional changes that can occur to the fetus as a result of medication. These effects are more subtle and more difficult to assess and therefore data to support or disprove associations is more limited (3). An example of fetotoxicity would be the association between NSAIDs and premature closure of the ductus arteriosus. Neurodevelopment disorders refer to the potential effects of drugs on cognitive function by interference with brain development. It is not known when specific functional neurodevelopmental effects occur. They are less obvious and harder to detect than structural malformations and a longer follow-up into childhood is required to detect them(4).

Teratogenesis initially described drug induced anatomical defects. This definition has been broadened by most authorities to include (5)

- Failure to implant and miscarriage
- Major and minor structural defects
- Intrauterine growth restriction
- Fetal death
- Postnatal effects

There may also be differences in genetic susceptibilities resulting in greater damage from a teratogenic exposure in one individual than another (1).

A “safe list” can be misleading as it implies that the agents on the list have been tested in humans for the full range of potential developmental toxicities including fetal death, structural malformations and functional deficits. Very few drug treatments have been

evaluated to the extent required to state that they are completely safe in pregnancy (Polifka and Friedman, 2002). It is worth noting that often the perception of both physicians and patients is that no amount of risk is acceptable and it is therefore important to advise the patient that all pregnancies have a 2-3% risk of congenital anomalies (Nielsen et al., 2014, Henderson and Mackillop, 2011).

Obvious ethical and logistical difficulties in studying drug safety among pregnant women have limited the amount of information available to women and their health care providers in choosing a drug for required treatment.

A single defect can have multiple causes, or multiple seemingly unrelated defects may have a common cause (Crider et al., 2009b).

Much of the research carried out on drug use in pregnancy involves retrospective case-control studies. These study types can only determine associations between exposure and birth defect and cannot determine causal relationships between exposure and defect or even underlying maternal infection (Crider et al., 2009b).

Data obtained from observational or case reports may be confounded by maternal co-ingestion of a number of drugs, at varying doses and for a range of indications. The severity of the underlying maternal condition, where relevant, is frequently unknown and information on other potential confounding variables may be incomplete. Also where exposure to medication is captured through prescription dispensing records e.g. Medicaid, compliance and therefore true exposure cannot be fully measured.

1.2 Safety in lactation an overview

The benefits of breastfeeding are well known. The immunological and nutritional value of breast milk to the infant is greater than that of formula feeds. These benefits are of particular importance for preterm infants. Although there are concerns that drugs taken by the mother might affect the infant, there is very little information or research available. In the absence of evidence of an effect, the potential for harm to the infant can be inferred from (7):

- The pharmacokinetic characteristics of the drug in the mother which determine the amount of active drug to which the infant is exposed.

- The pharmacokinetic capabilities of the infant with respect to absorption, distribution and elimination of the drug.

- The pharmacodynamics properties of the drug in the infant

For many drugs there is insufficient evidence available to offer unequivocal guidance, therefore, as in pregnancy, the prescriber should carefully consider the need for the medication and its effect on the infant before commencing treatment. A risk / benefit assessment must often be made whether to discontinue breastfeeding or to discontinue / abstain from medication use during lactation, taking into account the benefit of breastfeeding for the infant and mother and the benefit of therapy for the mother.

The use of unnecessary drugs should be avoided and the mother should be advised to limit the use of over the counter medication, and to seek advice if she is using them. Chemical properties of a drug influence transfer into breast milk e.g. lack of ionisation, small molecular weight, low volume of distribution, low maternal serum protein binding, and high lipid solubility all facilitate drug excretion into human milk (8). The prescriber should also consider the effect of the drug on breast milk production and the extent of oral absorption by the breastfed infant (9).

Particular attention should be paid to the need to breastfeed a premature infant. However, neonates and particularly premature infants are at a greater risk from exposure to drugs via breastmilk due to immature excretory function and the consequence of accumulation. Premature infants or neonates with an underlying chronic medical condition may be at a higher risk of adverse drug reactions compared to a more mature or healthier infant (10). Newborns have an immature immune system that renders them at high risk for infection while simultaneously reducing responses to most vaccines (11).

However, certain vaccines, such as Bacillus Calmette Guérin (BCG) and Hepatitis B vaccine (HBV), do demonstrate safety and some efficacy at birth, providing proof of principal that certain antigen-adjuvant combinations are able to elicit protective neonatal responses (11).

The amount of drug transferred in breast milk is rarely sufficient to produce a discernable effect on the infant (7). However, the infants may be exposed to sufficient levels of the drug to experience adverse effects or toxicity e.g. reduced sucking reflex with phenobarbital. Babies born prematurely or those suffering from jaundice are at a slightly higher risk of toxicity (7). All infants should be observed for potential problems that may occur with antimicrobial use in a breastfeeding mother.

The following should be monitored:

- Potential adverse effects or toxicity
- Modification of bowel flora leading to diarrhoea or candidiasis
- Interference with interpretation of culture results if fever work-up required
- Allergic response in a hypersensitive infant

A strategy to limit potential harm to the breastfed infant involves timing breastfeeding with respect to drug dosing so that peak serum / milk levels are avoided, that is choosing a regimen and route of administration which presents the minimum amount of drug to the infant. The administration of an immediate release formulation should be in the evening, wherever possible, after the last feed in order to limit the exposure during the nightly breastfeeding break. Note that this strategy would be ineffective for long-acting formulations or for multiple daily dosing regimens as there would be little variability in drug levels in breast milk. Multiple drug regimens may pose increased risk especially when adverse effects are additive e.g. nephrotoxicity. New drugs should be avoided if a therapeutically equivalent alternative that has been more widely used is available.

2 Antimicrobial safety in pregnancy and lactation

2.1 Antimicrobial safety in pregnancy and lactation monographs

- These monographs are intended as an adjunct to clinical knowledge and not a replacement and should be used in conjunction with other available information including, www.medicines.ie, www.hpra.ie, hospital medicine information centres, hospital pharmacy departments, the National Medicines Information Centre (NMIC) and other reference material.

- While the manufacturer's recommendations have been taken into consideration in compiling these monographs, current practice in maternity units is based on more detailed and specialised reference sources such as Reprotox, Lactmed, UKTIS, Briggs, Schaefer etc.

- As drug manufacturers and the Health Products Regulatory Authority (HPRA) update their recommendations from time to time, it is advisable to check www.medicines.ie and www.hpra.ie for the most up-to-date recommendations and licensing status.

- The FDA (Food and Drug Administration) have discontinued using their pregnancy labelling categories (A, B, C, D and X). This was due to the limitations of the system including over-simplistic categorisation of drug risk, the assumption that there is a graduated level of risk from one category to the next and also the lack of detail provided. The FDA now uses brief narrative summaries of pregnancy safety data (6).

2.2 Summary Monographs

2.2.1 Aciclovir

Pregnancy

Based on experimental animal studies and human experience, typical doses of aciclovir are not expected to increase the risk of congenital anomalies (12). Therapeutic doses of either

topical or systemic aciclovir are unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no risk (13, 14).
Current Irish National Guidelines state that "Women who experience a first episode of genital herpes in the first or second trimester should receive prophylactic antiviral medication throughout the third trimester (e.g. prophylactic dose - acyclovir 400mg twice daily or valacyclovir 500mg once daily)(15).

The current Irish Chicken Pox guidelines recommend (16)

- Oral aciclovir should be prescribed for pregnant women with chickenpox if they present within 24 hours of the onset of the rash and if they are more than 20 weeks of gestation.
- Aciclovir should be used with caution in early pregnancy and the risks and benefits should be discussed with the woman.
- Intravenous aciclovir should be given to all pregnant women with severe chickenpox, irrespective of when the rash developed

The Royal College of Obstetrics and Gynaecology in the UK have similar recommendations except they state that "Use of aciclovir should be considered before 20 weeks gestation. The risks and benefits of treatment should be discussed with the mother" (17).

Lactation

The American Academy of Paediatrics classifies aciclovir (aciclovir) as compatible with breastfeeding (18).

The UK Drugs in Lactation Advisory Service (UKDILAS) recommends the use of aciclovir in breastfeeding if clinically appropriate as it has poor oral bioavailability, the dose ingested by the infant from the breastmilk is small and it is used in full-term neonates from birth (19).

Aciclovir passes into breastmilk. Concentrations in breast milk have been shown to be higher than in plasma and this is thought to be due to a passive diffusion rather than an active transport mechanism (20, 21). Oral aciclovir is only approximately 20% absorbed (21) so even with the highest maternal dosages, the dosage of aciclovir in milk is equivalent to

only about 1% of a typical infant dosage and would not be expected to cause any adverse effects in breastfed infants. Topical aciclovir applied to small areas of the mother's body away from the breast should pose no risk to the infant (22).
Valaciclovir is an oral prodrug of aciclovir which is rapidly converted in to aciclovir. The dosage of aciclovir in milk after valaclovir is less than 1% of a typical infant dosage and would not be expected to cause any adverse effects in breastfed infants (22).

The Summary of Product Characteristics (SPC.) issued by the manufacturer state: (Zovirax®) "Following oral administration of 200 mg aciclovir five times a day, aciclovir has been detected in human breast milk at concentrations ranging from 0.6 to 4.1 times the corresponding plasma levels. These levels would potentially expose nursing infants to aciclovir dosages of up to 0.3 mg/kg bodyweight/ day. Caution is therefore advised if Zovirax® is to be administered to a nursing woman"(23).

2.2.2 Azithromycin

Pregnancy

Based on experimental animal studies and a limited number of human reports, azithromycin use during pregnancy is not expected to increase the risk of birth defects or adverse pregnancy outcome (12, 24). Antenatal use of this antibiotic has not been associated with a risk of pyloric stenosis, though a large retrospective American study found Ingestion of oral azithromycin placed young infants at an increased risk of developing pyloric stenosis with the association being strongest if the exposure occurred in the first 2 weeks of life (25).

Therapeutic doses of azithromycin are unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no risk (13). An increased incidence of cardiovascular defects and pyloric stenosis have been suggested for macrolides as a class, although causality has not been established conclusively (24).

Lactation

Due to the fact that low levels of azithromycin are detected in breast milk and that azithromycin is administered in infants in higher doses, it would not be expected to cause adverse effects in breastfed infants. Monitor the infant for possible effects on the

gastrointestinal flora, such as diarrhoea, candidiasis (thrush, nappy rash). Unconfirmed epidemiologic evidence indicates that the risk of hypertrophic pyloric stenosis in infants might be increased by maternal use of macrolide antibiotics during breastfeeding (22).

The SPC. Issued by the manufacturer state:
"Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterized the pharmacokinetics of azithromycin excretion into human breast milk" (26).

2.2.3 Cephalosporins

Pregnancy

Cephalosporins and penicillins are first line treatment options for appropriate indications in pregnancy, though whenever possible, older, well established cephalosporins should be used preferentially (21). Based on experimental animal and or human experience, cefalexin, cefaclor, cefotaxime and cefuroxime are not expected to increase the risk of congenital anomalies (12).

In experimental animal studies in rats, ceftriaxone did not increase the risk of congenital malformations (12). Two retrospective studies (one unpublished) have identified a possible association between in utero cephalosporin exposure and cardiovascular defects in offspring, with one study also suggesting an increased risk of oral clefts with in utero exposure to some cephalosporins (6, 27-29). A causal link between cephalosporin use in pregnancy and any congenital malformation remains to be proven (28).

Lactation

The American Academy of Paediatrics classifies cefotaxime and ceftriaxone as compatible with breastfeeding (6). UKDILAS states that the use of cefaclor, cefalexin and cefuroxime is acceptable in breastfeeding if clinically appropriate, but advises caution in the use of cefotaxime and ceftriaxone due to the fact that third generation cephalosporins have a greater potential to alter the gut flora (19). Lactmed states that cefalexin, cefaclor, cefuroxime, cefotaxime and ceftriaxone are acceptable to use during breastfeeding (22).

Limited information indicates that normally used doses produce low levels in milk that are not expected to cause adverse effects in breastfed infants. Occasionally, disruption of the infant's gastrointestinal flora, resulting in diarrhoea or thrush, has been reported with cephalosporins, but these effects have not been adequately evaluated (22). This may be more likely to occur if given intravenously, in high doses or over prolonged periods (19). Refer to the Lactmed database for guidance on the use of other cephalosporins in breastfeeding mothers.

The SPC. Issued by the manufacturer state: (sample Zinacef, cefuroxime)
"Cefuroxime is excreted in human milk in small quantities. Adverse reactions at therapeutic doses are not expected, although a risk of diarrhoea and fungus infection of the mucous membranes cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from cefuroxime therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman

2.2.4 Clarithromycin

Pregnancy

Most animal studies have not demonstrated evidence of reproductive toxicity, though there was some evidence of embryotoxicity including fetal death and growth restriction (6). Human data on early pregnancy exposure is limited to approximately 700 pregnancies (30, 31). The available data do not suggest an association between early pregnancy clarithromycin exposure and congenital anomalies. There was an increased rate of spontaneous miscarriage in clarithromycin-exposed pregnancies in one study, but this may have been related to differing maternal characteristics between the groups (30). A recent study in a separate population also found an increased hazard of miscarriage among women redeeming a prescription for clarithromycin in early pregnancy (31).

It would be reasonable, where alternative antimicrobials are available, to avoid clarithromycin in the first trimester of pregnancy (30). However, some authors do recommend clarithromycin as being compatible with pregnancy where resistance spectrum requires them or in case of penicillin allergy (6, 21). The antibiotic has not been associated

with an increased risk of pyloric stenosis (6). A small risk cannot be excluded, but a high risk of congenital anomalies in the children of women treated with clarithromycin during pregnancy is unlikely (13).

Lactation

Clarithromycin and its active metabolite, 14-hydroxy clarithromycin are excreted into breast milk (6). A 1993 study found that the combined exposure for an exclusively breastfed infant was about 2% of the mother's weight adjusted dose (6, 22, 32). Due to the low levels of clarithromycin and its active metabolite in breast milk and due to administration of clarithromycin directly to infants, both Lactmed® and *Schaefer et al* class clarithromycin use as acceptable in nursing mothers (21, 22).

UKDILAS advises caution in the use of clarithromycin in breastfeeding due to the potential risk of pyloric stenosis during macrolide use (19). The small amounts in milk are unlikely to cause adverse effects in the infant. Monitor the infant for possible effects on the gastrointestinal flora, such as diarrhoea, candidiasis (thrush, nappy rash). Unconfirmed epidemiologic evidence indicates that the risk of hypertrophic pyloric stenosis in infants might be increased by maternal use of macrolide antibiotics during breastfeeding (22).

The SPC.Issued by the manufacturer state: (Klacid)
"The safety of clarithromycin use during breastfeeding of infants has not been established. Clarithromycin is excreted into human breast milk" (23).

2.2.5 Clindamycin

Pregnancy

Based on experimental animal studies, clindamycin therapy during pregnancy is not expected to increase the risk of congenital anomalies (12). Although a small risk cannot be excluded, a high risk of congenital anomalies in the children of women treated with clindamycin during pregnancy is unlikely (13).

Lactation

The American Academy of Paediatrics classifies clindamycin as compatible with breastfeeding (6).
UKDILAS advises caution in the use of clindamycin in breastfeeding due to one case report of possible antibiotic induced colitis and limited published safety evidence (19).
Clindamycin has the potential to cause adverse effects on the breastfed infant's gastrointestinal flora. If oral or intravenous clindamycin is required by a nursing mother, it is not a reason to discontinue breastfeeding, however an alternate drug may be preferred. Monitor the infant for possible effects on the gastrointestinal flora, such as diarrhoea, candidiasis (thrush, nappy rash) or rarely, blood in the stool indicating possible antibiotic-associated colitis (22).

The SPC.Issued by the manufacturer state: Dalacin®
“Orally and parenterally administered clindamycin has been reported to appear in human breast milk in ranges from 0.7 to 3.8 µg/mL. Because of the potential for serious adverse reactions in nursing infants, clindamycin should not be taken by nursing mothers (IV. SPC). It is unlikely that a nursing infant can absorb a significant amount of Dalacin C from its gastrointestinal tract (PO SPC).” (23)

2.2.6 Co-amoxiclav

Pregnancy
Based on experimental animal studies and a small amount of published human experience, co-amoxiclav therapy during pregnancy is not expected to increase the risk of congenital anomalies (12, 33).

There are conflicting reports on the association between use of co-amoxiclav during pregnancy and an increased risk of neonatal necrotising enterocolitis (NEC) (34, 35).
Amoxicillin was associated in two studies with an increase in facial clefts (36, 37) . Most studies have not suggested an increase in malformations associated with this drug (12).
Penicillins are the antibiotics of choice for appropriate indications during pregnancy (21).

Lactation

UKDILAS and BNF state that the use of co-amoxiclav in breastfeeding is acceptable if clinically appropriate (7, 19)

Limited information indicates that serious reactions in infants are very uncommon during the use of amoxicillin-clavulanic acid during nursing, with restlessness, diarrhoea and rash occurring occasionally. If amoxicillin-clavulanic acid is required by the mother, it is not a reason to discontinue breastfeeding. Monitor the infant for these reactions during nursing (22).

The SPC.Issued by the manufacturer state (Augmentin®):
"Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breastfeeding might have to be discontinued. Amoxicillin/clavulanic acid should only be used during breastfeeding after benefit/risk assessment by the physician in charge" (23).

2.2.7 Erythromycin

Pregnancy

Based on most published human experience, erythromycin therapy during pregnancy has not been associated with an increase in the risk of birth defects. There is one human study suggesting a small increase in the risk of congenital heart disease and pyloric stenosis. This study was not confirmed in other samples (12).

Lactation

The American Academy of Paediatrics classifies erythromycin as compatible with breastfeeding (6). UKDILAS advises caution in the use of erythromycin in breastfeeding due to the potential risk of pyloric stenosis during macrolide use (19).

Due to the low levels of erythromycin in breast milk and safe administration directly to infants, it is acceptable in nursing mothers (22). The small amounts in milk are unlikely to cause adverse effects in the infant. Monitor the infant for irritability and possible effects on the gastrointestinal flora, such as diarrhoea, candidiasis (thrush, nappy rash) (22). One case

report and unconfirmed epidemiologic evidence indicates that the risk of hypertrophic pyloric stenosis in infants might be increased by maternal use of erythromycin during breastfeeding, but a causal relationship has not been confirmed (21, 22).

The SPC.Issued by the manufacturer state: Erythroped
“Erythromycin is excreted in breast milk, therefore, caution should be exercised when erythromycin is administered to a nursing mother” (23).

2.2.8 Ertapenem

Pregnancy

Ertapenem is a carbapenem antibiotic that is administered parenterally. There are no human data available (12). No epidemiological studies of congenital anomalies among infants born to women who were treated with ertapenem during pregnancy have been reported (13). Animal teratology tests performed by the manufacturer have not been published in the peer-reviewed literature (13).

Lactation

Lactmed states “Limited information indicates that single maternal doses of ertapenem up to 1 gram produce low levels in milk that are not expected to cause adverse effects in breastfed infants. Occasionally, disruption of the infant's gastrointestinal flora, resulting in diarrhoea or thrush has been reported with beta-lactams, but these effects have not been adequately evaluated” (22).

2.2.9 Fluconazole

Pregnancy

Fluconazole use during pregnancy has been associated through case reports with congenital anomalies similar to Antley-Bixler syndrome. Case reports do not establish causation. These cases occurred in association with high-dose and prolonged fluconazole therapy. Controlled studies in humans have not shown an increase in birth defect risk associated with fluconazole use at the lower exposure levels used for vaginal candidiasis (12). A low, single oral dose of fluconazole during pregnancy is unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no risk (13).

Lactation

The American Academy of Paediatrics classifies fluconazole as compatible with breastfeeding (6).

UKDILAS say that fluconazole is acceptable in nursing mothers because amounts excreted into breastmilk are less than the neonatal fluconazole dosage (19).

Although no adequate clinical studies on fluconazole in *Candida* mastitis have been published, a survey of members of the Academy of Breastfeeding Medicine found that fluconazole is often prescribed for nursing mothers to treat breast candidiasis, especially with recurrent or persistent infections. Treatment of the mother and infant simultaneously with fluconazole is often used when other treatments fail (22). Schaefer *et al* states " should systemic antifungal therapy be unavoidable, fluconazole, the best studied during breastfeeding, should be selected when the pathogen spectrum permits" (21).

The infant should be monitored for gastro-intestinal disturbances, especially if used for prolonged periods or in high doses, although these effects are unlikely to occur (19). The SPC. Issued by the manufacturer state: (Diflucan®):

"Fluconazole passes into breast milk to reach concentrations lower than those in plasma. Breastfeeding may be maintained after a single use of a standard dose 200 mg fluconazole or less. Breastfeeding is not recommended after repeated use or after high dose fluconazole" (23)

2.2.10 Fosfomycin

Pregnancy

No epidemiological studies of congenital anomalies among infants born to women treated with fosfomycin during pregnancy have been reported. Based on experimental animal studies and limited human experience which concentrated on efficacy more than safety, fosfomycin tromethamine therapy is not expected to increase the risk of congenital anomalies (6, 12). However it should be used with caution and under expert advice in pregnancy, particularly in the first trimester until further safety data is available.

Lactation

No reports describing the use of fosfomycin during human lactation have been located (6). However, consistent with the molecular weight, the drug is excreted into colostrum and breast milk (38). The risk to the nursing infant from exposure is unknown but modification of bowel flora may occur (6).

Fosfomycin should only be prescribed during breastfeeding when the primary, recommended antibiotics are insufficiently effective or not tolerated (21).

The SPC.Issued by the manufacturer state: (Monuril®):

“Fosfomycin is excreted into breast milk at low levels after a single injection. Therefore, fosfomycin can be used during breast feeding after a single oral dose (39).

2.2.11 Gentamicin

Pregnancy

Human studies with gentamicin use during pregnancy has been limited but have not suggested an increased risk of structural malformations (6, 12, 40). A small risk cannot be excluded, but there is no indication that the risk of malformations in children of women treated with gentamicin during pregnancy is likely to be great. Because it is an aminoglycoside, maternal gentamicin treatment during pregnancy may be associated with an increased risk for fetal auditory nerve or renal damage. This has not been widely demonstrated clinically to date in humans (12, 13). However 10 cases have been reported to Canadian regulator, so it may occur rarely, therefore ensure close monitoring of maternal levels (41).

Due to the limited available data and the theoretical toxicity risks, gentamicin use in pregnancy is generally reserved for serious or life threatening infections where standard antibiotic therapy has not been effective. If gentamicin is required, close monitoring of maternal serum concentrations is essential with dose amendment if required (40). See section on gentamicin therapeutic drug monitoring (chapter 12).

Lactation

The American Academy of Paediatrics classifies gentamicin as compatible with breastfeeding (18). However UKDILAS advises caution in the use of gentamicin in breastfeeding due to the potential risk of antibiotic induced colitis and the limited safety data. (19).

Small amounts of gentamicin are excreted into breast milk and absorbed by the nursing infant (6). A small study in 1994 found that gentamicin 80mg dose given three times daily by IM injection to the post-section mother produced a 3% maternal dose in breast milk and a 10% maternal serum level in the new born serum levels (42). This suggests that newborns to a degree that cannot be ignored, either absorb gentamicin enterally or accumulate due to reduced excretion (21). Serum levels with typical three times/day dosages are far below those attained when treating newborn infections and systemic effects of gentamicin are unlikely (22). Older infants would be expected to absorb even less gentamicin. As there is little variability in the milk gentamicin levels during multiple daily dose regimens, timing breastfeeding with respect to the dose is of little or no benefit in reducing infant exposure (22). Data are not available with single daily dose regimens. Monitor the infant for possible effects on the gastrointestinal flora, such as diarrhoea, candidiasis (e.g., thrush, nappy rash) or rarely, blood in the stool indicating possible antibiotic-associated colitis (22). As gentamicin is excreted primarily via the kidneys, caution and extra monitoring would be required when the infant has impaired renal function or is premature and in the newborn period.

Maternal use of an ear drop or eye drop that contains gentamicin presents little or no risk for the nursing infant (22). The SPC. Issued by the manufacturer state: (Gentacin ®) "Gentamicin is excreted in breast milk, but is unlikely to be a hazard to the infant except in the presence of maternal renal insufficiency when breastfeeding should be avoided, as the levels in breast milk then rise appreciably"(43).

2.2.12 Linezolid

Pregnancy

No epidemiological studies of congenital anomalies among infants born to women treated with linezolid during pregnancy have been reported. When toxic human doses (4 times human dose) were given to mice and rats, no evidence of congenital malformations were found, though decreased embryo viability, and decreased fetal weight (12). There is one case report in which a healthy baby was born to a woman who was treated with linezolid during the second trimester of pregnancy (13).

Lactation

UKDILAS advises caution in the use of linezolid in breastfeeding due no available published safety evidence (19).

Linezolid is excreted into breast milk in concentration likely to be effective against staphylococcal strains found in mastitis. Limited data indicate that the maximum dose an infant would receive through breast milk would be much less than the standard infant dose (22). The effects of linezolid exposure on a nursing infant are unknown, but myelosupression and reversible thrombocytopaenia are potential complications (6). Linezolid should only be prescribed during breastfeeding where the primary recommended antibiotics are insufficiently effective or not tolerated (21).

If linezolid is required by the mother, it is not a reason to discontinue breastfeeding. Monitor the infant for possible effects on the gastrointestinal tract, such as diarrhoea, vomiting, and candidiasis (e.g., thrush, nappy rash). However, because there is no published experience with linezolid during breastfeeding, an alternate drug may be preferred, especially while nursing a newborn or preterm infant (22).

The SPC.Issued by the manufacturer state: (Zyvox®)

“Animal data suggest that linezolid and its metabolites may pass into breast milk and, accordingly, breastfeeding should be discontinued prior to and throughout administration” (23).

2.2.13 Meropenem

Pregnancy

Briggs et *al* states “Two reports have described the use of meropenem in human pregnancy. Although the limited pregnancy experience does not allow a full assessment of the embryo-fetal risk, another carbapenem antibiotic is considered safe to use during the perinatal period (i.e. 28 weeks gestation or later) and most likely, meropenem can be classified similarly. The fetal risk before this period is unknown” (6).

Lactation

Although no information is available on the use of meropenem during breastfeeding, beta-lactams are generally not expected to cause adverse effects in breastfed infants (44). Occasionally, disruption of the infant's gastrointestinal flora, resulting in diarrhoea or thrush, has been reported with beta-lactams, but these effects have not been adequately evaluated (22). Until more human data is available, infants should be monitored for the most common adverse effects observed in adult patients – headache, constipation, diarrhoea, anaemia, vomiting and rash (6). Consistent with its molecular weight (about 384 Daltons) meropenem is excreted into breast milk (6). A case report in 2012 of a woman treated with meropenem 3g per day for 7 days starting 6 days postpartum, found that the theoretical maximum infant dose was 97 mcg/kg/day, which equates to 0.18% of the maternal weight adjusted dose, No dermatological or gastrological adverse effects were noted in the infant.

The SPC.Issued by the manufacturer state: (Meronem®):
“It is unknown whether meropenem is excreted in human milk. Meropenem is detectable at very low concentrations in animal breast milk. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from meropenem therapy taking into account the benefit of therapy for the woman”(23).

2.2.14 Metronidazole

Pregnancy

Older epidemiological data regarding maternal metronidazole use early in pregnancy and congenital anomalies have been summarized in two meta-analyses (45, 46). Although these analyses include different studies, the conclusions are the same - the risk of congenital anomalies does not appear to be increased among the infants of women who use vaginal metronidazole in the first trimester of pregnancy.

Some of the available reports have arrived at conflicting conclusions as to the safety of metronidazole in pregnancy, however, most of the published evidence suggests that metronidazole use during pregnancy does not represent a significant risk of adverse pregnancy outcome and structural defects to the fetus. (6, 12, 47).

Lactation

UKDILAS recommend caution in the use of metronidazole in breastfeeding. However, they state that "a short course or low dose regimen of maternal metronidazole can be commenced without interruption of normal breastfeeding routine". (19).

Schaefer *et al* states that when necessary, metronidazole may be used during breastfeeding. With intravenous treatment spread over several days, the administration should be, whenever possible, in the evening after the last feed in order to limit the exposure during the nightly breastfeeding break (21).

With maternal intravenous and oral therapy, breastfed infants receive metronidazole in doses that are less than those used to treat infections in infants, although the active metabolite adds to the total infant exposure (22). Plasma levels of the drug and metabolite are measurable, but less than maternal plasma levels. Case reports of candida infections and diarrhoea have been reported, and a comparative trial suggested that oral and rectal colonisation with Candida might be more common in infants exposed to metronidazole (22).

The SPC.Issued by the manufacturer state: (Flagyl®):

“Metronidazole should only be used during pregnancy or lactation following careful evaluation and only if considered essential by the physician. Its effects on fetal organogenesis are not known. If used, high dosage regimens should be avoided. The drug crosses the placenta and is excreted in breast milk in which concentrations equal those in serum. Unnecessary exposure to the drug should be avoided” (23).

If a single oral dose of metronidazole is used for trichomoniasis, the American Academy of Paediatrics recommends discontinuing breastfeeding for 12-24 hours to allow excretion of the drug (18), though other authors state that weaning or interruption of breastfeeding no longer seems justifiable based on the available experience (21).

2.2.15 Nitrofurantoin

Pregnancy

While some individual studies have suggested possible associations between nitrofurantoin therapy and congenital malformations, the available published data does not establish an increased risk of malformations or neonatal problems following exposure during pregnancy (48). Nitrofurantoin increased the incidence of congenital anomalies in mice at high exposure levels. An increase in malformations in human pregnancy has not been established, although an association of nitrosatable drugs with craniosynostosis was proposed. Haemolytic anaemia and increased jaundice have been reported in neonates (13, 49).

A population-based case control study using data from the US National Birth Defects Prevention study indicated that nitrofurantoin was significantly associated with anophthalmia/ microphthalmos, hypoplastic left heart syndrome, atrial septal defects and cleft lip with cleft palate (50). These associations may be chance findings due to multiple testing. As a result of this the American College of Obstetrics and Gynecology (ACOG) Committee on Obstetric Practice recommend that prescribing nitrofurantoin in the first trimester is appropriate when no other suitable alternative antibiotics are available (12, 50). Therapeutic doses of nitrofurantoin during pregnancy are unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no risk (12). Due to the

theoretical risk of haemolysis in neonates, nitrofurantoin is usually avoided after week 36 and where delivery is imminent. The BNF advises avoidance at term (7).

Lactation

The American Academy of Paediatrics classifies nitrofurantoin as compatible with breastfeeding (18).

Administration of nitrofurantoin directly to infants under 1 month of age and in those with G-6-PD deficiency is contraindicated because of potential haemolysis in these infants. Nitrofurantoin doses in milk are low and it can be used while breastfeeding older infants, but it is best to avoid it in infants under 1 month of age and those with G-6-PD deficiency at any age. Other than in these women, if nitrofurantoin is strongly indicated breastfeeding may continue (21).

The SPC.Issued by the manufacturer state: (Macrodantin®)

“Caution should be exercised while breastfeeding an infant known or suspected to have any erythrocyte enzyme deficiency as nitrofurantoin is detected in trace amounts in breast milk. Nitrofurantoin is contraindicated in infants under three months as well as pregnant women at term (in labour and delivery) because of the theoretical possibilities of haemolytic anaemia in the fetus” (51).

2.2.16 Penicillins

Pregnancy

Based on experimental animal studies and human experience, penicillins are not expected to increase adverse pregnancy outcome (12). There are over 25,000 published cases of amoxicillin use during pregnancy, no increased risks of spontaneous miscarriage, overall congenital malformation, intrauterine death or neonatal complications were identified in these analyses (52).

Amoxicillin was associated in two studies with an increase in facial clefts (37, 53). However, it is worth noting that in one of these study's the absolute risk for cleft lip/ palate increased from the baseline risk of 1-2 per 1,000 live births to 2-4 per 1,000 live births. This was a doubling of relative risk but quite a modest increase in absolute terms compared with the overall baseline risk of malformations at birth of about 30 per 1,000 (54).

Most studies have not suggested an increase in malformations associated with this drug (12). Penicillins are the antibiotics of choice during pregnancy (21). See individual manufacturers SPC for specific individual penicillin information (23, 55).

Lactation

UKDILAS recommends the use of amoxicillin, flucloxacillin, benzylpenicillin and phenoxymethylpenicillin in breastfeeding if clinically appropriate (19).

2.2.17 Amoxicillin

Amoxicillin is acceptable to use during breastfeeding. Limited information indicates that single maternal doses of amoxicillin 1 gram produce low levels in milk that are not expected to cause adverse effects in breastfed infants. Occasionally, rash and disruption of the infant's gastrointestinal flora, resulting in diarrhoea or thrush, have been reported, but these effects have not been adequately evaluated (22).

2.2.18 Benzylpenicillin

Penicillin G is acceptable to use during breastfeeding. Limited information indicates that single maternal doses of penicillin G of 4 million units intramuscularly produce low levels in milk that are not expected to cause adverse effects in breastfed infants. Occasionally, disruption of the infant's gastrointestinal flora, resulting in diarrhoea or thrush, has been reported with penicillins, but these effects have not been adequately evaluated (22).

2.2.19 Flucloxacillin

Limited information indicates that flucloxacillin levels in milk are low and are not expected to cause adverse effects in breastfed infants. Occasionally disruption of the infant's

gastrointestinal flora, resulting in diarrhoea or thrush have been reported with penicillins, but these effects have not been adequately evaluated (22).

2.2.20 Phenoxymethlypenicillin

Penicillin V is acceptable to use during breastfeeding. Limited information indicates that single maternal doses of penicillin V of 1320 mg produce low levels in milk that are not expected to cause adverse effects in breastfed infants. Occasionally, disruption of the infant's gastrointestinal flora, resulting in diarrhoea or thrush, has been reported with penicillins, but these effects have not been adequately evaluated (22).

In summary: Penicillin derivatives are the antibiotics of choice during breastfeeding (21). See individual manufacturers SPC for specific penicillin information (23, 55).

2.2.21 Piperacillin and tazobactam (Tazocin ®)

Pregnancy

Although the reported pregnancy experience with piperacillin-tazobactam is limited, all penicillins are considered low risk. Because tazobactam is a penicillin derivative, it is also probably safe in pregnancy and Reprotox® states that “Based on experimental animal data, tazobactam therapy is not expected to increase the risk of congenital anomalies” (12). No fetal harm in animals was observed when the piperacillin-tazobactam combination was used at doses close to those used in humans (6).

Lactation

UKDILAS advises caution in the use of piperacillin- tazobactam in breastfeeding due no available published safety evidence (19). Lactmed says that the use of piperacillin-tazobactum combination is acceptable during breastfeeding (22).

Although no information is available on the use of piperacillin and tazobactam during breastfeeding, limited information indicates that maternal doses of piperacillin produce low levels in milk that are not expected to cause adverse effects in breastfed infants. Occasionally, disruption of the infant's gastrointestinal flora, resulting in diarrhoea or

thrush, has been reported with penicillins, but these effects have not been adequately evaluated. Piperacillin and tazobactam is acceptable to use during breastfeeding (22). Owing to the high sodium content of this antibiotic, high doses may lead to hypernatraemia (7). Hale classifies the combination as L2, “drugs which have been taken by a large number of breastfeeding mothers without any observed increase in adverse effects in the infant and /or the evidence of a demonstrated risk which is likely to follow use of this medication in a breastfeeding woman is remote” (56),

The SPC. Issued by the manufacturer state: (Tazocin®):
“Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. Women who are breastfeeding should be treated only if the expected benefit outweighs the possible risks to the woman and child” (23).

2.2.22 Quinine

Pregnancy

The available data on standard therapeutic doses of quinine exposure in pregnancy do not demonstrate an increased teratogenic risk (57). The BNF states that adult treatment doses of oral and intravenous quinine e.g. 600mg every 8 hours orally, can be safely given to pregnant women (58) . Exposure in excess of 1.4g/dose has been associated with malformations in surviving infants (57). The risk with very large doses is primarily for deafness. Quinine might cause auditory nerve damage in fetuses exposed during pregnancy. Schaefer *et al* states “despite its toxicity, quinine belongs to the drugs of choice when dealing with chloroquine-resistant malaria tropica in pregnancy. “(21). Quinine containing analgesics and excessive or regular consumption of quinine containing drinks should be avoided during pregnancy (21).

Treatment with quinine has been reported to increase insulin secretion and prescribers should be vigilant for the associated risk of maternal hypoglycaemia (57). Untreated malaria in a pregnant woman poses a substantial risk to the fetus (13). A small risk cannot be excluded, but a high risk of congenital anomalies in the children of women treated with low therapeutic doses (300-500 mg/d) of quinine during pregnancy is unlikely (13).

Lactation

The American Academy of Paediatrics classifies quinine as compatible with breastfeeding (18). UKDILAS recommends the use of quinine in breastfeeding if clinically appropriate (19). Due to the low levels of quinine in breast milk, amounts ingested by the infant are small and would not be expected to cause any adverse effects in breastfed infants. The dosage in milk is far below those required to treat an infant for malaria. However, quinine should not be used in mothers with an infant who is glucose-6-phosphate dehydrogenase deficient (22). With malaria prophylaxis, the exposure for the infant may continue for considerably longer than with acute therapy. General recommendations are therefore more difficult and so limitation of breastfeeding should be decided on a case by case evaluation in consultation with a specialist. However, quinine is among the drugs for which there is most experience and it doesn't have substantial indications of potential for damage via the mother's milk (21).

The SPC. Issued by the manufacturer state: (Quinine sulphate tablets - Actavis®):
"Quinine sulphate is excreted into breast milk, but no problems in humans have been reported. However, quinine sulphate should not be given to nursing mothers unless the benefit outweighs the risk" (55).

2.2.23 Quinolones

Pregnancy

Ciprofloxacin and other fluoroquinolones are avoided during pregnancy and lactation due to cartilage toxicity in juvenile experimental animals, the difficulty in extrapolating animal teratogenicity results to humans and because interpretation of this toxicity is still controversial (6, 12). No adverse effects of ciprofloxacin use during human pregnancy have been documented (12)

The use of ciprofloxacin during human gestation does not appear to be associated with an increased risk of major congenital malformations (6). Therapeutic doses of ciprofloxacin during pregnancy are unlikely to pose a substantial teratogenic risk, but the data are

insufficient to state that there is no risk (13). Quinolones should only be used during pregnancy when no alternative agents are available with ciprofloxacin being the preferred option (21).

Lactation

Schaefer et al. states "Quinolones are **not** among the antibiotics of choice during breastfeeding. A standard antibiotic with a lower potential for risk can be used. When a complicated infection requires a quinolone, breastfeeding may continue. Ideally the most tested ciprofloxacin should be used"(21).

Quinolones include ciprofloxacin, levofloxacin, ofloxacin and nalidixic acid.
UKDILAS advises caution in the use of ciprofloxacin in breastfeeding due to limited published evidence of safety and one case report of pseudomembranous colitis (19).

The BNF states – "Avoid in infants with known G6PD deficiency due to the risk of haemolysis and use with caution in infants with epilepsy "(7). Monitor infant for gastro-intestinal disturbances and oral candida infection, especially if used in high doses, although these effects are unlikely to occur.

2.2.24 Ciprofloxacin

Fluoroquinolones have traditionally not been used in infants because of concern about adverse effects on the infants' developing joints. However, recent studies indicate little risk. Short-term use of ciprofloxacin is acceptable in nursing mothers. However, it is preferable to use an alternate drug for which safety information is available (22).

2.2.25 Ofloxacin

Fluoroquinolones have traditionally not been used in infants because of concern about adverse effects on the infants' developing joints. However, recent studies indicate little risk. Developmental problems have been reported in two infants exposed to ofloxacin in breastmilk, their mothers were also exposed to several drugs during pregnancy and during breastfeeding, so the problems cannot necessarily be attributed to ofloxacin (22).

Lactmed states that short-term use of ofloxacin is acceptable in nursing mothers. Avoiding breastfeeding for 4 to 6 hours after a dose should decrease the exposure of the infant to ofloxacin in breastmilk (22)

The SPC. Issued by the manufacturer state: (Ciproxin®):
“Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breastfeeding”(23).

2.2.26 Tetracyclines

Pregnancy

Tetracyclines are avoided during pregnancy (12). Exposure to tetracyclines in early pregnancy has not been firmly associated with any specific malformations. Exposure in the second or third trimester can cause discolouration of the deciduous teeth with staining of permanent teeth occurring with exposure after birth (12, 13, 59).

Schaefer *et al* suggests that all tetracyclines are contraindicated after the fifteenth gestational week as use might result in staining of teeth and possibly effects on bone growth. Experimental animal and epidemiology results have been inconsistent regarding possible increases in other abnormalities (13).

Tetracycline given intravenously might result in hepatic necrosis or the development of fatty liver in pregnant women (13). Therapeutic doses of doxycycline, tetracycline and oxytetracycline during pregnancy are unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no risk (13). Tetracyclines are not drugs of choice for treatment during pregnancy and should be avoided unless the indication is compelling (59).

Lactation

The American Academy of Paediatrics classifies tetracycline as compatible with breastfeeding (18). UKDILAS advises caution in the use of tetracyclines in breastfeeding due to limited published evidence of safety (19).

Tetracyclines include tetracycline, oxytetracycline, lymecycline, doxycycline and minocycline. The tetracyclines are broad-spectrum antibiotics whose value has decreased due to growing bacterial resistance. They are however still used for some infections e.g. chlamydia, brucella, rickettsia, brucella and the spirochaete (7).

A number of reviews have stated that tetracycline is contraindicated during breastfeeding because of possible staining of infants' dental enamel or bone deposition of tetracyclines. However, a close examination of available literature indicates that there is not likely to be harm in short-term use of tetracycline during lactation because milk levels are low and absorption by the infant is inhibited by the calcium in breast milk. *Schaefer et al* suggests that short-term use of tetracycline is acceptable in nursing mothers.
However, it has been suggested that doxycycline is bound less by calcium in milk, therefore it has increased infant absorption compared to other tetracyclines (19).
As a theoretical precaution, avoid prolonged or repeat courses during nursing. Monitor the infant for rash and for possible effects on the gastrointestinal flora, such as diarrhoea or candidiasis (thrush, nappy rash) (22).
Schaefer *et al* states “Should the antibiotics of choice not be appropriate, breastfeeding may continue with tetracycline use”. The BNF recommends that “ Tetracycline should not be given to breastfeeding women, although absorption and therefore discolouration of teeth in the infant is probably usually prevented by chelation with calcium in milk” (7).
With malaria prophylaxis, the exposure for the infant may continue for considerably longer than with acute therapy. General recommendations are therefore more difficult and so limitation of breastfeeding should be decided on a case by case evaluation in consultation with a specialist.

The SPC. Issued by the manufacturer state: (Doxycycline- Vibramycin®)
“The use of drugs of the tetracycline class during tooth development (pregnancy, infancy and childhood to the age of 12 years) may cause permanent discolouration of the teeth (yellow-grey-brown). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia

has also been reported. Vibramycin® is therefore contraindicated in these groups of patients. Tetracyclines are excreted into milk and are therefore contraindicated in nursing mothers" (23)

With malaria prophylaxis, the exposure for the infant may continue for considerably longer than with acute therapy. General recommendations are therefore more difficult and so limitation of breastfeeding should be decided on a case by case evaluation in consultation with a specialist. Pfizer, the manufacturers Vibramycin® contra-indicate its use in nursing mothers (23).

2.2.27 Trimethoprim

Pregnancy

Trimethoprim, a folic acid antagonist can cause abnormal embryo development in experimental animals. There are published data to suggest that trimethoprim use during fetal organogenesis may increase the risk of certain congenital malformations mediated by its folate antagonist effects (60).

Animal and human data also indicate that this increased risk may be mitigated against by the use of folic acid supplements (13, 60). Based on its mechanism of action and suggested associations with neural tube defects, cardiovascular defects, and facial clefts, trimethoprim is avoided during pregnancy, but a causal role for trimethoprim therapy in human birth defects has not been established (12).

Most of the reports of a positive association between trimethoprim exposure and congenital malformations were based on very small numbers of exposed women, therefore the findings should be interpreted with caution (60). Trimethoprim and co-trimoxazole should only be used in pregnancy where there are no alternatives (21). An increased risk of hyperbilrubinaemia should be considered in neonates who were exposed to co-trimoxazole peripartum, particularly if the infant is premature or has G6PD deficiency (60). There are certain situations where trimethoprim use in early pregnancy may be warranted e.g. *Pneumocystis carinii pneumonia* prophylaxis (with sulfamethoxazole).

Lactation

The American Academy of Paediatrics classifies the combination of trimethoprim-sulfamethoxazole as compatible with breastfeeding (18).

UKDILAS advises caution in the use of trimethoprim in breastfeeding due to limited published evidence of safety (19). Because of the low levels of trimethoprim in breastmilk, amounts ingested by the infant are small and would not be expected to cause any adverse effects in breastfed infants (22). Trimethoprim is used prophylactically in babies from one month with renal problems at a dose of 4mg /Kg twice a day (61). The SPC. Issued by the manufacturer state: (Monotrim®)

"Trimethoprim is excreted in breast milk. This should be kept in mind when considering administration to lactating women" (23)

2.2.28 Vancomycin

Pregnancy

Based on experimental animal studies, vancomycin is not expected to increase the risk of congenital malformations. There are a few human case reports with normal outcomes (12).

Lactation

UKDILAS recommends the use of vancomycin in breast feeding where clinically appropriate as small amounts appear in breast milk and vancomycin is not absorbed from the infant's gastrointestinal tract (19).

Limited information indicates that vancomycin produces low levels in milk. It would not be expected to be significantly absorbed following oral administration and it is unlikely to reach the bloodstream of the infant or cause any adverse effects in breastfed infants. No special precautions are required (22). Should treatment be unavoidable, breastfeeding may continue (21). Modification of the bowel flora, allergic responses or sensitization of the infant or interference with the interpretation of culture results, if a fever workup is required may occur in the infant as with other antimicrobials (6).

The SPC. Issued by the manufacturer state: (Vancomycin, Flynn Pharma®)

"Vancomycin hydrochloride is excreted in human milk. Caution should be exercised when vancomycin is administered to a nursing woman. It is unlikely that a nursing infant can absorb a significant amount of vancomycin from its gastro-intestinal tract" (23).

Table below summaries the probable safety of antimicrobials in breastfeeding. This Table should be used in conjunction with clinical judgement and the safety monographs included in this document.

2.3 Probable safety profile (in Infants) of antimicrobials in Lactation

Antimicrobial	**Probably safe**	**Caution** **Risk benefit analysis**	**Probably unsafe** **Or** **Unknown risk**	**Comment**
Aciclovir	√			
Azithromycin		√		Monitor for GIT effects
Cephalosporins	√			Caution cefixime & ceftazidime
Clarithromycin	√			Monitor for GIT effects
Clindamycin	√			Monitor for GIT effects
Co-amoxiclav	√			
Doxycycline		√		Consider safer alternative option before short term use if clinically required. Consult ID
Erythromycin		√		Case report pyloric stenosis
Fluconazole	√			
Fosfomycin	√			Use with caution or under expert advice
Gentamicin	√			Monitor for GIT effects
Linezolid		√		Monitor for GIT effects
Meropenem	√			Limited human data
Metronidazole		√		Monitor for GIT effects. Do not use high regimen e.g. 2g
Nitrofurantoin Not in G-6PD deficiency		√		Use alternative for infants under 1-3 months
Penicillins	√			
Pip-taz	√			
Quinine	√			
Quinolones		√		Limit exposure by avoiding breastfeeding for 3-4 hours after dose
Tetracycline			√	Short term use if

				clinically required
Trimethoprim		√		Folate antagonist-avoid use in 1st trimester
Vancomycin	√			

2.4 Appendix 1: Summary of current expert body recommendations -

Antimicrobial use during breastfeeding in healthy term infants

Antimicrobial	AAP[1] approved	UKDILAS[2] approved	Lactmed[3]	Hale Lactation risk category ** [4]
Aciclovir	yes	yes	Caution	L2
Azithromycin	n/a	Caution	Caution, monitor	L2
Cephalosporin 1st& 2nd generation Except cefuroxime	n/a	Yes	Yes	L1
Cephalosporin 3rd generation + cefuroxime	Yes	Caution	Yes	L2
Clarithromycin	n/a	Caution	Yes, monitor infant	L1
Clindamycin	Yes	Caution	Caution	L2
Co-amoxiclav	n/a	Yes	Yes	L1
Doxycycline	n/a	Caution	Caution, short courses	L3
Erythromycin	Yes	Caution	Yes	L3
Fluconazole	Yes	Yes	Yes	L3
Fosfomycin	n/a	n/a	Caution, limited data	L3
Gentamicin	Yes	Caution	Caution, monitor	L2
Linezolid	n/a	Caution	Caution, limited data	L3
Meropenem	n/a	Yes	Caution, limited data	L3
Metronidazole	n/a	Yes	Caution	L2
Nitrofurantoin	Yes	Caution	Yes , start 8 days after birth	L2
Penicillin	Yes	Yes	Yes	L1
Pip-taz	n/a	Caution	Yes	L2
Quinine	Yes	Yes	Caution	L2
Quinolones	n/a	Caution	Caution	L2/L3***
Tetracycline	Yes	Caution	Caution , short courses and monitor	L2
Trimethoprim	Yes*	Caution	No adverse effects expected	L3
Vancomycin	n/a	Yes	Caution, limited data	L1

*Refers to Co-trimoxazole combination **See appendix for Hale risk definitions (Version 2014)
***
L2 Ofloxacin and Levofloxacin; L3 Ciprofloxacin.

AAP = American Academy of Paediatrics; UKDILAS = UK Drugs in Lactation Advisory Service
Lactmed = American Safety in lactation database, available at http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

References:
1:(18)

2:(19)
3:(22)
4:(56)

2.5 Appendix 2: Hale's classification of lactation risk

Risk definition	Compatible	Probably Compatible	Possibly hazardous	Hazardous	Comment
L1	√				Used by large numbers of breastfeeding women without observed increase in adverse effects to infant. Controlled studies failed to show risk. Risk of harm remote
L2		√			Limited studies show no increase in adverse effects to infant or risk remote
L3		√			No controlled studies, though risk possible. Risk benefit analysis.
L4			√		Positive evidence of risk. Avoid unless benefit outweighs risk
L5				√	Significant risk. Risk outweighs benefit. Contraindicated

2.6 Antimicrobial safety in pregnancy complete monographs

2.6.1 Aciclovir

Based on experimental animal studies and human experience, typical doses of aciclovir are not anticipated to increase the risk of congenital anomalies (12). Therapeutic doses of either topical or systemic aciclovir are unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no risk (13, 14).

Information on the safety of first trimester exposure to aciclovir is mainly based on data from a pregnancy register managed by the manufacturer. This study reported the rate of major birth defects in 596 pregnancies exposed in the first trimester was 3.2%, similar to the background expected rate of 3.2% in the general population (62). Weaknesses of the study include the absence of a valid control group and recruitment relied on spontaneous reporting.

In a Danish, population based historical cohort study looking at first trimester exposure to acyclovir, valaciclovir and famciclovir and found no significant association between first trimester exposure to these antivirals and major birth defects (63). There were significant limitations in this study including the lack of long term outcomes, incomplete evaluation of maternal co-morbidity and compliance (so true exposure could not be measured) and the non-inclusion of spontaneous miscarriage and elective terminations.

The National Birth Defects Prevention Study found a significant increase in the risk of gastroschisis and reported use of antiherpetic medications (acyclovir, valaciclovir, or famciclovir) based on 14 cases of gastroschisis in which one of these agents had been used during early pregnancy. The authors noted that the data could not distinguish whether the increased risk of gastroschisis was related to antiherpetic medication use during early pregnancy or the underlying genital herpes infection for which it was indicated (64). No adverse effects in the fetus or new born attributable to the use of aciclovir during pregnancy have been reported (6, 14).

Congenital malformations have been reported in infants exposed during pregnancy, but they do not appear to be related to the drug (6). Systemic IV treatment is indicated for life-threatening disseminated herpes simples virus (HSV) infections to reduce the maternal , fetal and infant mortality of these infections (6). Oral aciclovir treatment of primary genital HSV infections also appear to be indicated to prevent adverse fetal outcomes, such as prematurity, intrauterine growth restriction (IUGR) and neonatal HSV infection (6).

Current Irish National Guidelines state that "Women who experience a first episode genital herpes in the first or second trimester should receive prophylactic antiviral medication throughout the third trimester (e.g. prophylactic dose - acyclovir 400mg BD or valacyclovir 500mg once daily)(15).

The current Irish Chicken Pox guidelines recommend (16)

- Oral aciclovir should be prescribed for pregnant women with chickenpox if they present within 24 hours of the onset of the rash and if they are more than 20 weeks of gestation.
- Aciclovir should be used with caution in early pregnancy and the risks and benefits should be discussed with the woman.
- Intravenous aciclovir should be given to all pregnant women with severe chickenpox, irrespective of when the rash developed

The Royal College of Obstetrics and Gynaecology in the UK have similar recommendations except they state that "Use of aciclovir should be considered before 20 weeks gestation. The risks and benefits of treatment should be discussed with the mother" (17).
The Summary of product Characteristics (SPC.) issued by the manufacturer state: (Zovirax ®): "The use of aciclovir should be considered only when the potential benefits outweigh the possibility of unknown risks. A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of Zovirax. The registry findings have not shown an increase in the number of birth defects amongst Zovirax exposed subjects compared with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause" (23).

2.6.2 Azithromycin

Based on experimental animal studies and a limited number of human reports, azithromycin use during pregnancy is not expected to increase the risk of birth defects or adverse pregnancy outcome (12, 24). The antibiotic has not been associated with a risk of pyloric stenosis. Therapeutic doses of azithromycin are unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no risk (13). An increased incidence of cardiovascular defects and pyloric stenosis have been suggested for macrolides as a class, although causality has not been established conclusively (24).

Azithromycin is in the macrolide antibiotic class that also includes erythromycin and clarithromycin. Animal studies have not suggested reproductive or teratogenic effects from gestational azithromycin exposure (6). Human data on early pregnancy exposures are reassuring (12, 65-67), though more data is available for other macrolides such as erythromycin (12, 65-67).

Studies have assessed the use of azithromycin later in pregnancy principally for the management of chlamydia cervicitis or prevention of preterm birth (68). One author suggests that azithromycin may be used in pregnancy when the resistance spectrum requires it or in cases of penicillin allergy (21). The UK Teratology Information Advisory Service recommend that as the number of documented exposures during pregnancy is limited, azithromycin should be avoided during pregnancy unless alternatives such as erythromycin are inappropriate (24).

The SPC. issued by the manufacturer state:
“There are no adequate data from the use of azithromycin in pregnant women. In reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observed. The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore azithromycin should only be used during pregnancy if the benefit outweighs the risk” (26).

2.6.3 Cephalosporins

Cephalosporins and penicillins are first line treatment options for appropriate indications in pregnancy, though whenever possible, older, well established cephalosporins should be used preferentially (21). Cefalexin, cefaclor, cefotaxime and cefuroxime are not expected to increase the risk of adverse pregnancy outcomes. (12) In experimental animal studies in rats, ceftriaxone did not increase the risk of congenital malformations (12).

Two retrospective studies (one unpublished) have identified a possible association between in utero cephalosporin exposure and cardiovascular defects in offspring, with one study also suggesting an increased risk of oral clefts with in utero exposure to some cephalosporins (6, 27-29). A causal link between cephalosporin use in pregnancy and any congenital malformation remains to be proven(28).

Cephalosporins include cefotaxime, cefalexin, cefuroxime, ceftriaxone and cefaclor. Cephalosporins cross the placenta and are detectable in the amniotic fluid at bactericidal concentrations (21). Animal studies with cephalosporins have not demonstrated any evidence of impaired fertility or harm to the fetus. More data are available for older agents. Data on several thousand early pregnancy exposures to cephalosporins are available in the literature. (6, 69). The rate of congenital anomalies does not appear to differ significantly from background rates. Although some data suggest an association with congenital malformations, most studies found that cephalosporin antibiotics, in general are safe in pregnancy (6). A population-based case-control study did not find an association between cephalosporin use during pregnancy and congenital anomalies (27).

The SPC. issued by the manufacturer state (sample -Zinacef – cefuroxime):
“There are limited amounts of data from the use of cefuroxime in pregnant women. Studies in animals have shown no reproductive toxicity. Zinacef should be prescribed to pregnant women only if the benefit outweighs the risk. Cefuroxime has been shown to cross the placenta and attain therapeutic levels in amniotic fluid and cord blood after intramuscular or intravenous dose to the mother” (23).

2.6.4 Clarithromycin

Clarithromycin produces adverse pregnancy outcome in experimental animals at low-order multiples of the human dose level on an mg/kg basis. Human experience has not suggested an increase in congenital anomalies in exposed pregnancies, but the number of cases of pregnancy exposure is small. Although it is not possible to conclude that clarithromycin therapy increases the risk of abnormal development, alternative antibiotics are recommended during pregnancy (12). However some authors do recommend clarithromycin as being compatible with pregnancy where resistance spectrum requires them or in case of penicillin allergy (6, 21). The antibiotic has not been associated with an increased risk of pyloric stenosis (6). A small risk cannot be excluded, but a high risk of congenital anomalies in the children of women treated with clarithromycin during pregnancy is unlikely (13).

Clarithromycin is in the macrolide antibiotic class that also includes erythromycin and azithromycin. Most animal studies have not demonstrated evidence of reproductive toxicity, though there was some evidence of embryotoxicity including fetal death and growth restriction (6, 70). Human data on early pregnancy exposures are limited to approximately 700 pregnancies. (30, 31, 65, 69, 71). The available data do not suggest an association between early pregnancy clarithromycin exposure and congenital anomalies.

There was an increased rate of spontaneous miscarriage in clarithromycin-exposed pregnancies in one study, but this may have been related to differing maternal characteristics between the groups (31). A recent study in a separate population also found an increased hazard of miscarriage among women redeeming a prescription for clarithromycin in early pregnancy but no increased risk for major malformations (21, 30) Two other studies found no increases risk of spontaneous miscarriage (65, 72). It would be reasonable, where alternative antimicrobials are available, to avoid clarithromycin in the first trimester of pregnancy.

The SPC. issued by the manufacturer state: (Klacid)

“The safety of clarithromycin during pregnancy has not been established. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk”(23).

2.6.5 Clindamycin

Based on experimental animal studies, clindamycin therapy during pregnancy is not expected to increase the risk of congenital anomalies (12). Although a small risk cannot be excluded, a high risk of congenital anomalies in the children of women treated with clindamycin during pregnancy is unlikely (13).
Animal data do not indicate a teratogenic risk with clindamycin (6, 12). Human data on clindamycin use in early pregnancy are available for approximately 1000 women (69, 73). There is no indication that early pregnancy use is associated with congenital anomalies, however the data are limited. There is more experience of clindamycin use later in pregnancy to prevent preterm birth (74). Pseudomembranous enterocolitis is a dangerous maternal complication of clindamycin treatment that may also happen after vaginal application (21).

The SPC. issued by the manufacturer state: (Dalacin ®):
“Oral and subcutaneous reproductive toxicity studies in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus due to clindamycin, except at doses that caused maternal toxicity. Animal reproduction studies are not always predictive of human response.

Clindamycin crosses the placenta in humans. After multiple doses, amniotic fluid concentrations were approximately 30% of maternal blood concentrations. Benzyl alcohol which is present in many IV preparations of clindamycin can cross the placenta and cause fetal toxicity. In clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters has not been associated with an increased frequency of congenital abnormalities. There are no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy. Clindamycin should be used in pregnancy only if clearly needed”.

2.6.6 Co-amoxiclav

Co-amoxiclav is a combination product that contains amoxicillin and clavulanic acid. Based on experimental animal studies and a small amount of published human experience, co-amoxiclav therapy during pregnancy is not expected to increase the risk of congenital anomalies (12, 33). There are conflicting reports on the association between use of co-amoxiclav during pregnancy and an increased risk of neonatal necrotising enterocolitis (NEC) (34, 35). Amoxicillin was associated in two studies with an increase in facial clefts. Most studies have not suggested an increase in malformations associated with this drug (12). Penicillins belong to the antibiotics of choice during pregnancy (21).

Several studies have described the use of amoxicillin and potassium clavulanate for various infections in women. Most studies have observed no adverse effects in the fetus or new born attributable to the combination (6). Schaefer *et al* states" Penicillins belong to the antibiotics of choice during pregnancy. Where bacterial resistance studies are indicated, penicillins may be combined with clavulanic acid if required" (21).

In the Oracle children's study, in women who received either co-amoxiclav and or erythromycin and did not have PPROM, the study suggested that there may be a small increased risk of functional impairment and cerebral palsy in the children of women who took antibiotics because of early premature labour without rupture of membranes (75). These findings are difficult to interpret as there was no increased risk of cerebral palsy in women with PROM. Cerebral palsy is unlikely to be a direct effect of the antibiotics but may be due to factors involved in prolonging a pregnancy that might otherwise have delivered early (33).

The SPC. issued by the manufacturer state (Augmentin ®):
"Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development. Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the fetal membrane it was reported that prophylactic treatment with

amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician" (23).

2.6.7 Co-amoxiclav and necrotizing enterocolitis (NEC)

There are conflicting reports on the association between use of co-amoxiclav during pregnancy and an increased risk of neonatal necrotising enterocolitis (NEC) (34, 35). This had led to an ongoing debate about late pregnancy antibiotic exposure and the risk of NEC (76).

Concerns about the use of co-amoxiclav in pregnancy either alone or in combination with erythromycin were raised by the ORACLE studies which demonstrated a significant increased incidence of NEC when it was given in preterm pre-labour rupture of membranes (34), and a non-significant increase when used during spontaneous preterm labour with intact membranes (75). This association was noticed in the analysis of secondary outcomes (34, 75). Further to the publication of these studies, concern was raised about the use of co-amoxiclav antenatally and further study was recommended, particularly in its use in the neonatal period.

Al-Sabbagh et al studied the association between perinatal exposure and an increased risk of NEC in their case-control study from 1983-2000 in Liverpool's women's hospital (35). They found no evidence that there was a link between co-amoxiclav exposures antenatally and development of NEC.(35).

There has been considerable discussion about the findings of the Oracle trials from an inference (77) and statistical (78) perspective and from conclusions drawn (79, 80).

The mechanism for the apparent association of co-amoxiclav exposure and NEC is unclear. It has been suggested that co-amoxiclav may encourage colonic overgrowth with antibiotic resistant Gram-negative organisms, such as *Enterobacter* spp, *Citrobacter* spp, and

Pseudomonas spp and reduce the numbers of protective Gram-positive and anaerobic bacteria (80).

The conclusions drawn from the Oracle trials have also affected recommendations in other areas of obstetrics. Extrapolating from the Oracle trial data, the UK National Institute for Health and Clinical Excellence (NICE) Guideline Developing Group (GDG) For Caesarean Sections cite a hypothetical increased risk of necrotising enterocolitis by fetal exposure to co-amoxiclav if it is given as prophylaxis before skin incision or cord-clamping at the time of caesarean section. Therefore the recommendation is that co-amoxiclav is not used for surgical prophylaxis prior to Caesarean sections (81, 82). As alternatives to co-amoxiclav potentially have an equivalent risk of causing necrotising enterocolitis due to their similar spectrums of activity e.g. cefuroxime and metronidazole but also have the added maternal risk of causing C. *difficile* infection (76), there seems to be no simple solution.

Further research is needed urgently address the use of co-amoxiclav to provide clear evidence-based guidance on the most appropriate and safest use of co-amoxiclav in pregnancy and to re-evaluate the risk associated with co-amoxiclav compared with other antibiotics so that this issue is resolved (76).

2.6.8 Ertapenem

Ertapenem is a carbapenem antibiotic that is administered parenterally. It is structurally related to the beta-lactam antibiotics and belongs to the same class as meropenem. Ertapenem did not interfere with embryo development in pregnant mice given 3 times and rats given 1.2 times the human dose on a surface area basis. Fertility was also not impaired at these dose levels in these species. In a mouse pregnancy study, there was some effect on fetal weight at the highest dose level (12). There are no human data available (12).

2.6.9 Erythromycin

Based on most published human experience, erythromycin therapy during pregnancy has not been associated with an increase in the risk of birth defects. Erythromycin is in the macrolide antibiotic class that also includes clarithromycin and azithromycin. An animal

study did not demonstrate any teratogenic effects of gestational erythromycin use (83). Data on over 15,000 thousand early pregnancy exposures to erythromycin are available in the literature (6, 69, 84-87). The rate of congenital anomalies does not differ significantly from background rates.

A Swedish study suggested that early pregnancy erythromycin use is associated with cardiovascular defects and pyloric stenosis, though the authors note that the level of risk for an individual exposed pregnancy is still low (88). An update of this Swedish study verified an association between the use of erythromycin during early pregnancy and cardiovascular effects, though most defects were mild and the cause of the association remains unclear (89). Other studies did not support these findings (72, 90) (66, 91-93).

In the National Birth Defects Prevention Study which reviewed prenatal antibacterial medication use and the incidence of birth defects, erythromycin use was associated with an increase in anencephaly (7 exposed cases, adjusted OR 2.04, 95% CI 1.1-5.3) and transverse limb deficiency (9 exposed cases, adjusted OR 2.1, 95% CI 1.0-4.2), although the latter finding was not statistically significant. This study included multiple comparisons, which might have given rise to the findings by chance (90). A similarly designed case-control study from the Slone Epidemiology Centre did not identify an association between erythromycin use during pregnancy and major malformations as a group or several subtypes of malformation including cardiac and neural tube defects (93).

In the Oracle children's study, in women who received either co-amoxiclav and or erythromycin and did not have PPROM, the study suggested that there may be a small increased risk of functional impairment and cerebral palsy in the children of women who took antibiotics because of early premature labour without rupture of membranes (75). These findings are difficult to interpret as there was no increased risk of cerebral palsy in women with PROM. Cerebral palsy is unlikely to be a direct effect of the antibiotics but may be due to factors involved in prolonging a pregnancy that might otherwise have delivered early (33).

The SPC. issued by the manufacturer state: (Erythroped ®).

“There are no adequate and well-controlled studies in pregnant women. However, observational studies in humans have reported cardiovascular malformations after exposure to medicinal products containing erythromycin during early pregnancy.

Erythromycin has been reported to cross the placental barrier in humans, but fetal plasma levels are generally low” (23).

2.6.10 Fluconazole

Fluconazole use during pregnancy has been associated through case reports with congenital anomalies similar to Antley-Bixler syndrome. Case reports do not establish causation. These cases occurred in association with high-dose and prolonged fluconazole therapy. Controlled studies in humans have not shown an increase in birth defect risk associated with fluconazole use at the lower exposure levels used for vaginal candidiasis (12). A low, single oral dose of fluconazole during pregnancy is unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no risk (13).

It is not known if fluconazole crosses the human placenta, though its molecular weight (about 360) would suggest that it does (6). There was a report of three children (two of them siblings) with craniofacial, skeletal and cardiac malformations, after first trimester exposure to fluconazole, similar to those seen in animal studies (94). Additional case reports have described two births involving craniofacial, limb and cardiac defects in two mothers who used fluconazole (95, 96).

However other studies have not found evidence of an increased risk malformations after fluconazole exposure in the first trimester (97-99). Danish cohort studies based on a prescription register could not find an increased risk of birth defects after first trimester exposure in several thousand women (99, 100) An extended analysis of Danish data observed an increased risk for tetralogy of Fallot based on seven cases, though the risk of major birth defects was not increased (101). Schaefer et al states “If a systemic treatment with an azole derivative antifungal becomes absolutely necessary, fluconazole is one of the preferred as the better tested medications. If possible, treatment should start after the first trimester” (21).

The SPC. issued by the manufacturer state: (Diflucan ®):
“Data from several hundred pregnant women treated with standard doses (<200mg/day) of fluconazole, administered as a single dose or a repeated dosage in the first trimester, show no undesired effects in the fetus. There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were being treated for at least three or more months with high dose (400 - 800 mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole use and these events is unclear. Studies in animals have shown reproductive toxicity.
Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary. Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections” (23).

2.6.11 Fosfomycin

Based on experimental animal studies and limited human experience which concentrated on efficacy more than safety, fosfomycin tromethamine therapy is not expected to increase the risk of congenital (6, 12). However it should be used with caution under expert advice in pregnancy, particularly in the first trimester until further safety data is available.

Fosfomycin is a broad spectrum antibiotic that is bactericidal by inhibiting the synthesis of the bacterial cell wall. Fosfomycin trometamol is an orally active salt used for the treatment of uncomplicated UTI (21).

Fosfomycin crosses the placenta at term, with fetal blood concentrations reaching levels about two-third those of the mother two or more hours after drug ingestion (102). Preclinical teratology studies in rats and rabbits did not identify an increase in malformations with maternal oral dose levels up to 1400 mg/kg/day and 420 mg/kg/day, respectively (103). Some authors recommend the oral use of fosfomycin during pregnancy (104, 105).

These studies, however are primarily focused on the effectiveness of fosfomycin and not on the risk to the new born (21). Overall the experience argues against a teratogenic and fetotoxic potential in humans (21), however we have no early pregnancy exposure outcome data.

The SPC. issued by the manufacturer state: (Monuril ®)
“At the present time, single-dose antibacterial treatments are not suitable to treat urinary tract infections in pregnant women. Animal studies do not indicate reproductive toxicity. A large amount of data concerning effectiveness of fosfomycin during pregnancy is available. However, only moderate amounts of safety data on pregnant women is available and available evidence does not indicate any malformative or feto/neonatal toxicity of fosfomycin” (39).

2.6.12 Gentamicin

Human experience with gentamicin use during pregnancy has been limited but has not suggested an increased risk of structural malformations (6, 12, 40). A small risk cannot be excluded, but there is no indication that the risk of malformations in children of women treated with gentamicin during pregnancy is likely to be great. Because it is an aminoglycoside, maternal gentamicin treatment during pregnancy may be associated with an increased risk for fetal auditory nerve or renal damage. This has not been widely demonstrated clinically to date in humans (12, 13). However 10 cases have been reported to Canadian regulator, so it may occur rarely, therefore ensure close monitoring of maternal levels (41).

Due to the limited available data and the theoretical toxicity risks, gentamicin use in pregnancy is generally reserved for serious or life threatening infections where standard antibiotic therapy has not been effective. If gentamicin is required, close monitoring of maternal serum concentrations is essential with dose amendment if required (40).

Aminoglycosides include gentamicin, amikacin and tobramycin. These drugs have a narrow therapeutic window and incorrect dosing carries the risk of significant toxicity, primarily nephrotoxicity and ototoxicity.

As gentamicin may cause reversible nephrotoxicity and irreversible ototoxicity, its use is reserved for severe infections during pregnancy. Gentamicin has not been associated with reproductive toxicity or congenital anomalies in animal studies, however dose-related nephrotoxicity has been reported in rats (6). Ototoxicity, known to occur after gentamicin therapy, has not been reported as an effect of in utero exposure (6).

Aminoglycosides cross the placenta and there are reports of fetal eighth cranial nerve toxicity with permanent bilateral deafness after in utero exposure to other aminoglycosides, e.g. streptomycin. The population based dataset of the Hungarian Case Control Surveillance of Congenital Anomalies, covering 1980-1996 was used to evaluate the teratogenicity of aminoglycoside antibiotics (IV gentamicin, streptomycin, tobramycin and oral neomycin) in a study published in 2000. The investigators concluded that there was no detectable teratogenic risk for structural defects of any of the aminoglycosides (106). Limited human data do not suggest that early pregnancy gentamicin exposure is associated with congenital anomalies (106)
To avoid additive nephrotoxicity, co-administration of gentamicin with other nephrotoxic drugs should be avoided if possible, and separated by the longest period possible if concurrent use is necessary (7). Excretion of aminoglycosides is primarily via the kidney and accumulation occurs in renal impairment. Ototoxicity and nephrotoxicity occur commonly in patients with renal failure. If there is renal impairment, the interval between doses must be increased, if the impairment is severe, the dose must be reduced also. A once-daily, high dose regimen of an aminoglycoside should be avoided in patients with a creatinine clearance less than 20mL/minute.

The BNF 68 (British National Formulary) states that there is insufficient evidence to recommend a once daily, high dose regimen of an aminoglycoside in pregnancy (7). The Royal College of Obstetrics and Gynaecology (RCOG) includes "gentamicin as a single dose of 3-5mg/kg in their bacterial sepsis in pregnancy table on antimicrobials “(Table 5) they do not

however, state that they recommend any of the drugs in the table or provide any evidence for single dose gentamicin (107) .

The SPC. issued by the manufacturer state: (Gentacin ®).
“Safety for use in pregnancy and lactation has not been established. Gentamicin crosses the placenta and there is a risk of ototoxicity (auditory or vestibular nerve damage) in the fetus. Gentamicin should only be used where the seriousness of the mother's condition justifies the risk and use is considered essential by the physician. In such cases, serum gentamicin concentration monitoring is essential” (43).

2.6.13 Linezolid

No epidemiological studies of congenital anomalies among infants born to women treated with linezolid during pregnancy have been reported. Linezolid does not cause congenital malformations in mice and rats at dose levels causing maternal toxicity, decreased embryo viability, and decreased fetal weight (12). There is one case report in which a healthy baby was born to a woman who was treated with linezolid during the second trimester of pregnancy (13).

Linezolid is a reversible monoamine oxidase inhibitor and therefore interactions occur when administered concurrently with other monoamine oxidase inhibitors, monoamines such as adrenaline and noradrenaline or tyramine containing food and drinks.

Animal studies have demonstrated some fetotoxicity, but no increase in congenital anomalies (12). Human data on linezolid exposure during pregnancy are limited to a case report of successful treatment of pneumonia at 14 weeks’ gestation, with no evidence of harm in the neonate (108). There are insufficient data on the use of linezolid in pregnant women to determine safety. Weekly blood counts should be performed as maternal myelosupression may occur. Linezolid should only be used during pregnancy for severe maternal infections where no alternative is available (21). If no alternatives are available and linezolid must be used, the maternal benefit appears to outweigh the unknown fetal risk (6).

Linezolid is a reversible non-selective monoamine oxidase inhibitor (MAOI), women should follow normal precautions for MAOI use and avoid consuming large quantities of tyramine – rich foods including mature cheese, yeast extracts, undistilled alcoholic beverages etc.(7). Concurrent treatment with SSRIs (selective serotonin reuptake inhibitors) and linezolid is contraindicated (23)

The SPC. issued by the manufacturer state: (Zyvox ®)
"There are no adequate data from the use of linezolid in pregnant women. Studies in animals have shown reproductive toxicity. A potential risk for humans exists. Linezolid should not be used during pregnancy unless clearly necessary i.e. only if the potential benefit outweighs the theoretical risk" (23).

2.6.14 Meropenem

Briggs et al states "Two reports have described the use of meropenem in human pregnancy. Although the limited pregnancy experience does not allow a full assessment of the embryo-fetal risk, another carbapenem antibiotic is considered safe to use during the perinatal period (i.e. 28 weeks gestation or later) and most likely, meropenem can be classified similarly. The fetal risk before this period is unknown" (6).

Meropenem is a broad-spectrum carbapenem antibiotic given IV and is normally reserved for severe refractory infections. The drug belongs to the same class of antibiotics as imipenem. Animal data suggests low risk and the BNF suggests "use only if potential benefit outweighs risk" (7). Schaefer et al states "Animal studies and human experience do not show malformations or other undesirable effects. However, systematic investigations have not been conducted" (21)

The SPC. issued by the manufacturer state: (Meronem ®):
"There are no or limited amount of data from the use of meropenem in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive

toxicity. As a precautionary measure, it is preferable to avoid the use of meropenem during pregnancy" (23).

2.6.15 Metronidazole

Although some of the available reports have arrived at conflicting conclusions as to the safety of metronidazole in pregnancy, most of the published evidence suggests that metronidazole use during pregnancy does not represent a significant risk of adverse pregnancy outcome and structural defects to the fetus. (6, 12, 47).

Animal studies have not consistently indicated that metronidazole is associated with developmental toxicity. Studies of metronidazole use in early pregnancy involving over 2500 women have not indicated that it is associated with congenital anomalies. (12, 69, 109). Precautions relating to the use of metronidazole during pregnancy, particularly at earlier gestations relate to evidence of mutagenicity in bacteria and carcinogenicity in animals (6). There are no human data that indicate that gestational metronidazole exposure is mutagenic or carcinogenic. Although treatment in the first trimester was traditionally avoided, some clinical guidelines note that there is no evidence of teratogenicity from the use of metronidazole in early pregnancy (110) and recommend treatment of women with symptomatic bacterial vaginosis (111) or Trichomoniasis (110, 112) at any stage of pregnancy.

The SPC. issued by the manufacturer state: (Flagyl ®):
"Metronidazole should only be used during pregnancy or lactation following careful evaluation and only if considered essential by the physician. Its effects on fetal organogenesis are not known. If used, high dosage regimens should be avoided. The drug crosses the placenta and is excreted in breast milk in which concentrations equal those in serum. Unnecessary exposure to the drug should be avoided" (23).

2.6.16 Nitrofurantoin

While some individual studies have suggested possible associations between nitrofurantoin therapy and congenital malformations, the available published data does not establish an

increased risk of malformations or neonatal problems following exposure during pregnancy (48). Nitrofurantoin increased the incidence of congenital anomalies in mice at high exposure levels. An increase in malformations in human pregnancy has not been established, although an association of nitrosatable drugs with craniosynostosis was proposed.

Haemolytic anaemia and increased jaundice have been reported in neonates (13, 49). Haemolytic anaemia has been reported in a newborn infant whose mother was treated with nitrofurantoin shortly before delivery (13). Nordeng also detected a significantly higher rate of neonatal jaundice among nitrofurantoin exposed neonates compared with unexposed controls and suggested that nitrofurantoin should be used with caution in the last 4 weeks of pregnancy until more data are available (49).

Animal studies have not consistently implicated nitrofurantoin as a cause of adverse fetal effects (one high dose study in mice indicated a slight increase in congenital anomalies) (6). The risk of major malformations in general or of specific malformations was not significantly increased among 1,329 infants and abortuses whose mothers had been given a prescription for nitrofurantoin during the first trimester of pregnancy in an Israeli population-based record linkage study (113). This study has the advantage of including live births, stillbirths and terminations.

A population-based case control study using data from the US National Birth Defects Prevention study indicated that nitrofurantoin was significantly associated with anophthalmia/ microphthalmos, hypoplastic left heart syndrome, atrial septal defects and cleft lip with cleft palate (90). These associations may be chance findings due to multiple testing. These findings are not supported by a previous case-control study (114).

An American College of Obstetricians and Gynecologists Committee Opinion concluded that it is still considered appropriate to use nitrofurantoin in the first trimester when no other suitable alternative antibiotics are available, and that nitrofurantoin remains a first line agent for urinary tract infections later in pregnancy (50). First trimester nitrofurantoin exposure was associated with congenital anomalies, principally cardiac septal defects in a

Swedish study (69). A similar Norwegian study with 1,334 women who were dispensed nitrofurantoin in the first trimester did not find any association between exposure and the occurrence of congenital anomalies, though there was a slightly increased risk of neonatal jaundice after use in the last 30 days. There was no association with cardiac defects (49). This links in with previous concerns about nitrofurantoin exposure and fetal haemolysis. Nitrofurantoin is often used during pregnancy and fetal haemolysis has not been commonly observed, therefore a significant risk is not likely, though if possible it should be avoided towards the end of pregnancy (21).
The incidence of congenital malformations was found to be within the expected range in a hospital based, multi-centre double blind, placebo-controlled RCT comparing the efficacy of a 1 day nitrofurantoin regimen to a 7 day nitrofurantoin regimen in the treatment of asymptomatic bacteriuria during pregnancy (115).

A more recent study found that first trimester exposure to nitrofurantoin was not associated with increased risk for total major congenital malformations or with specific malformations (90, 113). A Danish study demonstrated an association between nitrofurantoin exposure and cerebral palsy, however this association was also present for unrelated antimicrobials (116). The authors suggest that underlying infections are the causal factor rather than medication exposures. Goldberg et al suggest that despite conflicting information, nitrofurantoin should only be used in the first trimester if there are no other suitable alternative antibiotics (113).

Therapeutic doses of nitrofurantoin during pregnancy are unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no risk (12).

The SPC. issued by the manufacturer state: (Macrodantin ®)
“Based on animal reproduction studies and clinical experience in humans over many years, there is no evidence of any teratogenic effects of nitrofurantoin on the fetus. As with all drugs, maternal side effects should they occur, may adversely affect the course of the pregnancy. The drug should be used at the lowest effective dose only after careful assessment of benefit versus potential risk. Nitrofurantoin is contraindicated in pregnant women at term (during labour and delivery) ”(51).

2.6.17 Penicillins

Based on experimental animal studies and human experience, penicillins are not believed to increase adverse pregnancy outcome (12). There are over 25,000 published cases of amoxicillin use during pregnancy, no increased risks of spontaneous miscarriage, overall congenital malformation, intrauterine death or neonatal complications were identified in these analyses (52). Amoxicillin was associated in two studies with an increase in facial clefts (37, 53). However, it is worth noting that in the first study, the absolute risk for cleft lip/ palate increased from the baseline risk of 1-2 per 1,000 live births to 2-4 per 1,000 live births, quite modest in absolute terms compared with the overall baseline risk of malformations at birth of about 30 per 1,000 (54). Most studies have not suggested an increase in malformations associated with this drug (12). Penicillins belong to the antibiotics of choice during pregnancy (21). See individual manufacturers SPC for specific penicillin information (23, 55).

Penicillins include benzylpenicillin, phenoxymethylpenicillin, flucloxacillin, ampicillin and amoxicillin. They are sometimes available in combination formulations e.g. co-amoxiclav and piperacillin-tazobactam (See separate monographs). There are extensive reassuring human data on the use of penicillins during pregnancy , with that BNF 68 stating that all the above “are not known to be harmful during pregnancy”(7). In thousands of studied pregnancies over the past decades, no indications were seen to show that treatment with penicillins is embryo or foeto-toxic (86, 117-119). Two studies have demonstrated that early pregnancy amoxicillin exposure is associated with the occurrence of oral clefts (37, 53). The limitations of these studies including recall bias, non-responder bias and differential ascertainment of exposure data for cases and controls mean that the practice of prescribing amoxicillin in early pregnancy remains appropriate where there is an appropriate indication. The association between amoxicillin exposure and oral clefts has not been reported in large population-based registry studies from Denmark (120) and Sweden (Bengt Källén, Personal Communication, June 2013). Penicillins are first line treatment options for appropriate indications in pregnancy.

Pregnant women who are treated with penicillins for syphilis may develop the Jarisch-Herxheimer reaction – a febrile reaction, often with headache and myalgia. Fetal monitoring is recommended in these cases, as uterine contractions may occur (121).

Please see medicines.ie for specific penicillin / penicillin derivatives (23).

2.6.18 Piperacillin and tazobactam

Although the reported pregnancy experience with piperacillin-tazobactam is limited, all penicillins are considered low risk. Because tazobactam is a derivative of the penicillin nucleus, it is also probably safe in pregnancy and Reprotox® states that "Based on experimental animal data, tazobactam therapy is not expected to increase the risk of congenital anomalies" (12). No fetal harm in animals was observed when exposed to this combination at doses close to those used in humans (6).

Piperacillin, a derivative of ampicillin, is a broad spectrum penicillin. Animal reproduction studies in mice and rats at doses up to 4 times the human dose have shown no evidence of impaired fertility or fetal harm (6). Tazobactam, a β-lactamase inhibitor, is combined with piperacillin to increase its antibacterial spectrum. Tazobactam is not available as a single agent, and is a derivative of the penicillin nucleus. Owing to the high sodium content of this antibiotic, high doses may lead to hypernatraemia (7).

The SPC. issued by the manufacturer state: (Tazocin ®):
"There are no or a limited amount of data from the use of Tazocin in pregnant women. Studies in animals have shown developmental toxicity, but no evidence of teratogenicity, at doses that are maternally toxic.
Piperacillin and tazobactam cross the placenta. Piperacillin / tazobactam should only be used during pregnancy if clearly indicated, i.e. only if the expected benefit outweighs the possible risks to the pregnant woman and fetus" (23).

2.6.19 Quinine

The available data on standard therapeutic doses of quinine exposure in pregnancy do not demonstrate an increased teratogenic risk (57). Exposure in excess of 1.4g/dose has been associated with malformations in surviving infants (57). The risk with very large doses is primarily for deafness. Quinine might cause auditory nerve damage in fetuses exposed during pregnancy.

Schaefer et al states “despite its toxicity, quinine belongs to the drugs of choice when dealing with chloroquine-resistant malaria tropica in pregnancy.“ (21). Quinine containing analgesics and excessive or regular consumption of quinine containing drinks should be avoided during pregnancy (21). Treatment with quinine has been reported to increase insulin secretion and prescribers should be vigilant for the associated risk of maternal hypoglycaemia (57). Untreated malaria in a pregnant woman poses a substantial risk to the fetus (13). A small risk cannot be excluded, but a high risk of congenital anomalies in the children of women treated with low therapeutic doses (300-500 mg/d) of quinine during pregnancy is unlikely (13).

Quinine is the oldest antimalarial agent. It works well and effectively against the erythrocytic forms of all Plasmodium species. Quinine has effectively been replaced by newer agents for the treatment of malaria. Despite a relatively high toxicity and a narrow therapeutic range, it is used again increasingly in the treatment of chloroquine resistant Plasmodium falciparum malaria (21, 122).

Many of the available studies that report the occurrence of congenital anomalies after first trimester exposure to quinine relate to cases where high doses of quinine were used in unsuccessful spontaneous miscarriage attempts (6, 12). The malformations noted are varied, although CNS anomalies and limb defects are the most common. Other studies have reported auditory and optic nerve damage, again these reports usually concern the use of quinine in toxic doses as an abortifacient (6).

A study reviewed in abstract followed 150 pregnant women treated with quinine for malaria and found a statistically significant increase in their plasma insulin concentrations and

decrease in plasma glucose concentrations. Gestational ages at time of treatment were not clear from the abstract (123). Studies with pregnant women exposed to quinine during the first trimester have found no evidence of an increased risk of spontaneous miscarriage or preterm delivery, congenital malformations, still birth or low birth weight with the use of standard dosage of quinine for the treatment of acute malaria (124-126).

The SPC. issued by the manufacturer state: (Quinine sulphate tablets - Actavis ®):
"Quinine may cause congenital abnormalities of the CNS and extremities following administration of large doses during pregnancy, phototoxicity and deafness have been reported in neonates. Quinine should not be used in pregnancy unless benefits outweigh risks.
For the treatment of malaria, pregnancy in a patient is not generally regarded as a contraindication to the use of quinine. As malaria infection is potentially serious during pregnancy and poses a threat to the mother and fetus, there appears to be little justification in withholding treatment in the absence of a suitable alternative.
Quinine sulphate should not be used during pregnancy to treat leg cramps" (55).

2.6.20 Quinolones

Ciprofloxacin and other fluoroquinolones are avoided during pregnancy and lactation due to cartilage toxicity in juvenile experimental animals, the difficulty in extrapolating animal mutagenicity results to humans and because interpretation of this toxicity is still controversial (6, 12). No adverse effects of ciprofloxacin use during human pregnancy have been documented (12). The use of ciprofloxacin during human gestation does not appear to be associated with an increased risk of major congenital malformations (6). Therapeutic doses of ciprofloxacin during pregnancy are unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no risk (13). Quinolones are antibiotics of second choice during pregnancy in situations when better studied antibiotics are ineffective with ciprofloxacin being the preferred option (21).

Quinolones include ciprofloxacin, levofloxacin, ofloxacin and nalidixic acid. Most data is available for ciprofloxacin and to a lesser extent ofloxacin and levofloxacin (21). A recent

review of the safety of quinolones in pregnancy is reassuring (127). However this study as with many other drug use in pregnancy reviews is hampered by the lack of RCT data, incomplete confounder information and small sample size. Quinolones have a high affinity for cartilage and bone tissue which is highest in immature cartilage (21). Unlike other organs, the skeleton is progressively developing through the entire gestational period and even more prominently in the later stages of pregnancy and well beyond childhood and puberty. Quinolones have been demonstrated to cause cartilage damage in animal studies (6).

As quinolones act as DNA synthesis inhibitors, there were initial concerns about potential embryotoxic effects. A meta-analysis including approximately 1500 quinolone-exposed pregnancies suggested that exposure was not associated with major malformations (128). Data from the Swedish Medical Birth register with over 1000 exposures are also reassuring. Although a number of birth defects have occurred in the offspring of women who have taken ciprofloxacin during pregnancy, the lack of a pattern among the anomalies is reassuring, however a causal relationship cannot be ruled out (6). Padberg et al in their prospective observational cohort study in 2014 found that the rate of major birth defects after first trimester exposure to fluoroquinolones, except moxifloxacin, was not increased compared to the unexposed group (129). They observed a trend towards an increased risk of birth defects with Moxifloxacin and recommended a detailed fetal ultrasound if first trimester exposure occurred (129).
It is preferable to avoid quinolones during pregnancy, however the use of quinolones may be appropriate where no alternative treatment options are available, for example in cases of patient allergy or resistance strains. Considering the limited data available and the fact that diseases urgently requiring quinolone treatment are rare, it appears advisable to use safer alternatives such as penicillins, cephalosporins etc. as antibiotics of choice where possible. The BNF 68 suggests “a single dose of ciprofloxacin may be used for the prevention of a secondary case of meningococcal meningitis” (7).

The SPC. issued by the manufacturer state: (Ciproxin ®).
“The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate

direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / fetus. As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy" (23).

2.6.21 Tetracyclines

Tetracyclines are best avoided during pregnancy (12). There is varying advice on avoidance of tetracycline exposure, with some authors advising avoidance from after the fifth week of pregnancy (130) and others advising that exposure after week 12 is associated with adverse outcomes (69). Exposure to tetracyclines in early pregnancy has not been firmly associated with any specific malformations but use in the second or third trimester can cause discolouration of the deciduous teeth and possibly effects on bone growth, with staining of permanent teeth occurring with exposure after birth (12, 13, 21, 59). Experimental animal and epidemiology results have been inconsistent regarding possible increases in other abnormalities (13). Therapeutic doses of doxycycline, tetracycline and oxytetracycline during pregnancy are unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no risk (13). Tetracyclines are not drugs of choice for treatment during pregnancy and should be avoided unless the indication is compelling (59)

Tetracyclines include tetracycline, oxytetracycline, doxycycline, lymecycline and minocycline. These agents were used commonly during pregnancy after being introduced in the 1950s , but this use was sharply curtailed after it became clear that tetracyclines can discolour the deciduous teeth when used after the 25th week of gestation (12). Numerous reports from the 1950s indicated that gestational exposure to tetracyclines led to staining of children's teeth, tooth enamel defects and effects on the growth of long bones. (130). Tetracyclines form a complex with calcium orthophosphate which from the sixteenth week of pregnancy when fetal mineralisation occurs, can bind to calcium ions and become incorporated into bones and teeth undergoing calcification (6, 21).

The BNF states “When travel to malarious areas is unavoidable during pregnancy, doxycycline can be used for malaria prophylaxis if other regimens are unsuitable and if the entire course is completed before 15 weeks gestation (unlicensed use)” (7). Based on experimental animal studies and human reports, doxycycline is not anticipated to increase the risk of congenital anomalies (12). Doxycycline is avoided during pregnancy because other tetracyclines have been associated with transient suppression of bone growth and with staining of developing teeth (12).

An association between doxycycline/tetracycline exposure in the second month of pregnancy and oral clefts has been reported, however this was based on only two exposed cases and may have been explained by multiple testing (120). Cooper in his 2009 retrospective cohort study, which included 30,049 infants (total no. exposed = 24,521, number exposed to doxycycline 1843) from Tennessee Medicaid born between 1985 and 2000 looked at the effect of first trimester exposure to four antimicrobials recommended for potential bioterrorism attacks (azithromycin, ciprofloxacin, doxycycline, amoxicillin and positive control - erythromycin) in pregnant women. The authors concluded there was no significantly increased risk of congenital malformations associated with fetal exposure to any of the study antimicrobials during the entire pregnancy (86).

Tetracycline given intravenously might result in hepatic necrosis or the development of fatty liver in pregnant women (13). Many women reported to have developed this complication had been treated for pyelonephritis, and it is possible that renal impairment is a contributor to this toxic effect. The mobilization of tetracycline from bone during pregnancy has been suggested as a possible toxic mechanism for some cases of fatty liver during pregnancy (12).

The SPC. issued by the manufacturer state: (Doxycycline- Vibramycin ®)

“Vibramycin ® is contraindicated in pregnancy. The use of drugs of the tetracycline class during tooth development (pregnancy, infancy and childhood to the age of 12 years) may cause permanent discolouration of the teeth (yellow-grey-brown). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Vibramycin ® is therefore contraindicated in these groups of patients.

It appears that the risks associated with the use of tetracyclines during pregnancy are predominantly due to effects on teeth and skeletal development. Vibramycin ® has not been studied in pregnant women. It should not be used in pregnancy unless, in the judgement of the physician, it is essential for the welfare of the woman.
Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy" (23).

2.6.22 Trimethoprim

Trimethoprim, a folic acid antagonist can cause abnormal embryo development in experimental animals. There are published data to suggest that trimethoprim use during fetal organogenesis may increase the risk of certain congenital malformations mediated by its folate antagonist effects (60). Animal and human data also indicate that this increased risk may be mitigated against by the use of folic acid supplements (13, 60) Based on its mechanism of action and suggested associations with neural tube defects, cardiovascular defects, and facial clefts, trimethoprim is avoided during pregnancy, but a causal role for trimethoprim therapy in human birth defects has not been established (12). Most of the reports of a positive association between trimethoprim exposure and congenital malformations were based on very small numbers of exposed women, therefore the findings should be interpreted with caution (60). Trimethoprim and co-trimoxazole are antibiotics of second choice throughout pregnancy (21). An increased risk of hyperbilrubinaemia should be considered in neonates who were exposed to co-trimoxazole peripartum, particularly if the infant is premature or has G6PD deficiency (60).

Trimethoprim acts as a folate antagonist and should be used with caution in early pregnancy. Animal studies have demonstrated that trimethoprim exposure may lead to congenital anomalies or fetal death and human studies have demonstrated an increased risk of congenital anomalies including cardiovascular and neural tube defects (6).

A Danish nationwide cohort study (1997-2000) found a doubling of congenital malformations in offspring of women exposed to trimethoprim in the 12 weeks before

conception (131). There was a significant increase in major malformations of the heart (OR = 2.49; 1.18-5.26) and limbs (OR = 2.18; 1.13-4.23)(131).A further study using the same Danish National Prescription registry cohort (1996-2008) also indicated that trimethoprim exposure in the three months before pregnancy was associated with a higher overall risk of congenital anomalies. (132)
The same nationwide cohort indicated that trimethoprim exposure in the first trimester is associated with a doubling in the risk of miscarriage (133). It is not clear that these data were adjusted for the indication that required drug therapy, which might have been a factor in causing a miscarriage (12).

A case-control study of infants with oral clefts, cardiovascular defects, or urinary tract defects found a significant association with a group of folic acid antagonists that included trimethoprim. The risk of cardiovascular defects was significantly lower among exposed women who took folic acid supplements (134).

There are certain situations where trimethoprim use in early pregnancy may be warranted e.g. *Pneumocystis carinii pneumonia* prophylaxis (with sulfamethoxazole). Adequate folate supplementation is required. However, in light of recent literature, a detailed risk-benefit analysis should be carried out. An increased risk of preterm birth and low birth weight has been reported after exposure to trimethoprim/ sulfamethoxazole (135, 136). A systematic review and meta-analysis concluded that the overall pooled prevalence of congenital anomalies across 24 studies including 4196 women receiving trimethoprim/ sulfamethoxazole in pregnancy did not differ from background population rates.

As sulphonamides e.g. sulfamethoxazole compete with bilirubin for binding sites with plasma proteins, it has been argued that the risk of neonatal kernicterus is increased when sulphonamides are given at the end of gestation. With current surveillance, the danger of kernicterus is low (21). However, a rise in bilirubin, especially in premature infants, cannot be excluded when sulphonamides have been used until birth (21). However, a Danish population based study found no association between sulfamethozole exposure near term and an increased risk of neonatal jaundice (137).

Where possible, first trimester use of trimethoprim should be avoided in women at risk of folic acid deficiency or those who are taking another folate antagonist (60).

The SPC. issued by the manufacturer state: (Monotrim ®)
“Monotrim use in contraindicated during pregnancy”(23).

2.6.23 Valaciclovir

Valaciclovir is an oral prodrug of aciclovir which is rapidly converted in to aciclovir. Based on experimental animal studies and a small number of human reports, valaciclovir therapy is not expected to increase the risk of congenital anomalies.

Use during the last month of human pregnancy has been reported to be without adverse neonatal effects (12). Although the experience with valaciclovir in early pregnancy is limited, many studies have reported the use of aciclovir during all stages of pregnancy. Based on the combined data, there is no evidence of a major risk to the human fetus from valaciclovir or aciclovir, though long-term follow-up of children exposed in utero to these agents is warranted (6).

The SPC. issued by the manufacturer state: (Valtrex ®):
“A limited amount of data on the use of valaciclovir and a moderate amount of data on the use of aciclovir in pregnancy is available from pregnancy registries (which have documented the pregnancy outcomes in women exposed to valaciclovir or to oral or intravenous aciclovir (the active metabolite of valaciclovir); 111 and 1246 outcomes (29 and 756 exposed during the first trimester of pregnancy, respectively) and post marketing experience indicate no malformative or feto/neonatal toxicity. Animal studies do not show reproductive toxicity for valaciclovir. Valaciclovir should only be used in pregnancy if the potential benefits of treatment outweigh the potential risk” (23).

2.6.24 Vancomycin

Based on experimental animal studies, vancomycin is not expected to increase the risk of congenital malformations. There are a few human case reports with normal outcomes (12).

Vancomycin is an antibiotic used for gram-positive bacteria when either the organisms' are resistant to less toxic agents or the patient is sensitive to these agents. Vancomycin is often reserved for treatment of MRSA, multi-resistant enterococci and life threatening bacterial infections to avoid the development of resistance and to prevent the selection of vancomycin-resistant enterococci (VRE) (21). Vancomycin crosses the placenta reaching the fetus in relevant quantities and has not been shown to be teratogenic in animal studies (21). No epidemiological studies of congenital anomalies in infants born to women who took vancomycin during pregnancy have been reported (6, 13). Reyes et al studied the offspring of 10 women treated for varying period in the 2nd and 3rd trimester with 1g intravenously every 12 hours. There was no increase in malformations, auditory impairment or nephrotoxicity associated with drug exposure (138).

Monitoring of vancomycin plasma levels is essential to reduce the risk of fetal toxicity (7). When Vancomycin is administered by too rapid an infusion, "red man syndrome" may develop. This syndrome is characterised by pruritus, shortness of breath, flushing, headache and rarely hypotension with accompanying fetal bradycardia (6).

The SPC. issued by the manufacturer state: (Vancomycin, Flynn Pharma ®)
"Teratology studies have been performed at 5 times the human dose in rats and 3 times the human dose in rabbits and have revealed no evidence of harm to the fetus due to vancomycin. In a controlled clinical study, the potential ototoxic and nephrotoxic effects of vancomycin hydrochloride on infants were evaluated when the drug was administered to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancomycin hydrochloride was found in cord blood.

No sensorineural hearing loss or nephrotoxicity attributable to vancomycin was noted. One infant, whose mother received vancomycin in the third trimester, experienced conductive hearing loss that was not attributable to vancomycin.

Because vancomycin was administered only in the second and third trimesters, it is not known whether it causes fetal harm. Vancomycin should be given in pregnancy only if clearly needed and blood levels should be monitored carefully to minimise the risk of fetal toxicity. It has been reported, however, that pregnant patients may require significantly increased doses of vancomycin to achieve therapeutic serum concentrations" (23).

2.7 Useful websites

- National Clinical Guidelines in Obstetrics and Gynaecology. Available from http://www.hse.ie/eng/about/Who/clinical/natclinprog/obsandgynaeprogramme/obsgyneguide.html
- Health Protection Surveillance Centre. Available at http://www.hpsc.ie/
- The Health Products Regulatory Authority. Available from : https://www.hpra.ie/
- UK Teratology Information Service (UKtis) abstracts: Available at http://www.uktis.org/html/maternal_exposure.html. Subscription required for full text.
- Reproductive Toxicology Center. REPROTOX Washington [cited 2015 July]. Available from: www.reprotox.org.
- Royal College of Obstetrics and Gynaecology. Available from: www.rcog.org.uk
- Medicines.ie. Medicines.ie Available from: www.medicines.ie.

2.7.1 Current update status for Websites accessed and referenced

Drug use in Pregnancy website reference audit trail

	Date of last update of monograph		
	Reprotox	**Teris**	**Uktis**
Aciclovir	09/05/2015	03/2011	12/2010
Valaciclovir	23/07/2015	n/a	n/a
Azithromycin	13/01/2015	03/2011	09/2012
Cephalosporins			05/2012
Cefalexin	16/07/2015	04/2013	n/a
Cefaclor	06/07/2015	09/2013	n/a
Cefotaxime	11/06/2015	11/2010	n/a
Cefuroxime	09/05/2015	08/2007	n/a
Ceftriaxone	09/05/2015	n/a	n/a
Clarithromycin	22/01/2015	02/2011	09/2012
Clindamycin	27/03/2015	02/2014	n/a
Co-amoxiclav	12/06/2015	02/2014	06/2012
Erythromycin	08/07/2015	12/2009	07/2012
Fluconazole	16/05/2015	10/2012	04/2014
Fosfomycin	09/04/2015	n/a	n/a
Gentamicin	07/06/2015	05/2015	06/2012
Linezolid	23/06/2015	01/2015	n/a
Meropenem	n/a	n/a	n/a
Metronidazole	01/03/2015	05/2012	12/2013
Nitrofurantoin	01/01/2015	02/2014	06/2012
Penicillins		07/2012	09/2012
Amoxicillin	16/07/2015	02/2014	09/2014
Flucloxacillin/Dicloxacillin	17/07/2015	04/2014	06/2012
Penicillin-G (Benzylpen.)	09/07/2015	01/2010	06/2012
Penicillin-V (Phenoxymethylpen.)	09/07/2015	01/2010	06/2012
Piperacillin-tazobactam	20/07/2014	n/a	n/a
Quinine	17/07/2015	01/2010	10/2013
Quinolones			06/2012
Ciprofloxacin	08/11/2014	12/2014	06/2012
Ofloxacin	19/05/2015	n/a	n/a
Levofloxacin	01/11/2014	n/a	n/a
Tetracyclines			
Doxycycline	08/07/2015	02/2011	06/2012
Oxytetracycline	04/03/2015	02/2011	06/2012
Tetracycline	04/03/20105	09/2013	06/2012
Trimethoprim	19/02/2015	05/2012	12/2013
Vancomycin	14/03/2015	12/2012	n/a

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