Best Practice & Research Clinical Obstetrics and Gynaecology 57 (2019) 106–119

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

8

Drugs in renal disease and pregnancy

Asif Sarwar, Advanced Clinical Pharmacist - Electronic Prescribing, MPharm, DipClin(Hosp)

Advanced Clinical Pharmacist – Electronic Prescribing, Pharmacy Department, University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Birmingham, B15 2TH, England, United Kingdom

Keywords:
Chronic kidney disease
Foetotoxicity
Teratogenicity
Pregnancy safety
Lactation

A B S T R A C T

This review aims to summarise historic and the latest evidence of commonly used drugs in pregnant women with chronic kidney disease (CKD). Data regarding safety of drugs in breastfeeding are also described. Practical recommendations are made on the use of newer agents that have limited information of use in pregnant women with CKD. Pharmacokinetic and dynamic issues are outlined, and general principles for prescribing drugs in pregnant women with CKD are listed. Resources to investigate drug safety are presented.

Introduction

A number of considerations have to be made when prescribing drugs in pregnancy, which are summarised in the British National Formulary [1]. The importance of pre-pregnancy counselling in women with CKD who are considering pregnancy cannot be underestimated. Ideally, such conversations need to highlight the relevant risks and modifications of drug therapies in advance of conception.

The following general principles apply to prescribing drugs in pregnant women with renal disease [2]:

- Prescribe only if expected benefit is thought to be greater than the risk to the foetus (e.g. clinically significant infections)

E-mail address: asif.sarwar@uhb.nhs.uk.

https://doi.org/10.1016/j.bpobgyn.2019.03.006
1521-6934/

Table 1
Anti-hypertensives.

Drug	First trimester	Second trimester	Third trimester	Pregnancy Comments	Breastfeeding
ACE inhibitors and At-II antagonists	Probably safe	Avoid	Avoid	Advice regarding angiotensin-converting enzyme inhibitors (ACEIs) is to avoid during the second and third trimesters. Association with growth retardation, renal failure, respiratory distress, foetal hypotension and intrauterine death has been demonstrated [5,6]. As these effects are thought to be directly related to the pharmacological effects, the recommendations extrapolate to angiotensin II receptor (At-II) antagonists.	Safety data available for captopril and enalapril [7].
Labetalol	Safe	Safe	Safe	Licensed for pregnancy. Consider other comorbidities, e.g. asthma. It is well documented that labetalol is a very valuable anti-hypertensive agent in pregnancy. It provides good blood pressure lowering effects without adversely affecting uterine or renal blood flows. It is the first-line treatment for hypertension in pregnancy as recommended by NICE guideline 107 [8].	Safe
Beta-blockers	Safe	Safe	Safe	Although there have been concerns about the use of beta-blockers [9,10], two Cochrane reviews found that beta-blockers are effective at reducing the risk of severe hypertension and the need for additional agents [11,12]. The reviews also noted that there was no statistically significant risk for small-for-gestational age births nor preterm birth in comparison to methyldopa.	Metoprolol and atenolol safe
Nifedipine	Safe	Safe	Likely safe	A Swedish registry study looked at abnormalities associated with calcium channel blockers in the first trimester [13]. Of the 217 pregnancies studied, three babies were born with heart defects, which the authors concluded was too small a risk to be specific to the drugs. Furthermore, a prospective study by the Motherisk program reported no abnormalities in 43 out of 44 women treated with nifedipine [14]. The use of nifedipine for severe hypertension has been documented in two studies from the 1980s [15,16]. The latter study noted that babies born to mothers treated with nifedipine in the latter stage of pregnancy were associated with lower birth weights.	Safe

(*continued on next page*)

Table 1 (*continued*)

Drug	First trimester	Second trimester	Third trimester	Pregnancy Comments	Breastfeeding
Calcium channel blockers (excluding nifedipine)	Safe	Likely safe	Avoid	A multicentre cohort study in Europe followed up 229 pregnancies of women exposed to calcium channel blockers (CCBs). No difference in pregnancy outcomes was seen, although there was an increased rate of miscarriage, preterm birth and lower birth weight seen with CCBs [17]. Third-trimester use of CCBs has been associated with a 3.6% increased risk of neonatal seizures, jaundice and haematological disorders, which may be due to placental transfer of the drugs, resulting in low infant cellular calcium levels [16].	Safe
Methyl-Dopa	Safe	Safe	Safe	Avoid use in depression or if risk of depression.	Avoid in all due to risk of post-natal depression [8].
Diuretics	Safe	Safe	Safe	Diuretics can theoretically reduce plasma volume and lead to intra-uterine growth retardation. This was not seen in a Cochrane review from 2007, although caution is still recommended to use the lowest doses to avoid electrolyte disturbances [18].	

Table 2
Immunosuppressants.

Drug	First trimester	Second trimester	Third trimester	Pregnancy Comments	Breastfeeding
Glucocorticosteroids	Safe	Safe	Safe	There are reports of increased risks of intra-uterine growth retardation with prolonged courses. Foetal adrenal suppression has been seen with maternal doses >15 mg/day, although this has been refuted in a single-centre case series (n = 16) [19]. Some studies have noted an increased risk of orofacial clefts [20,21], although this not been confirmed in more recent studies [22].	Compatible. There have only been very small concentrations of steroid detected in milk
Azathioprine	Safe	Safe	Use with caution	Azathioprine has been associated with low birth weight and prematurity in some studies, but outcomes may be more reflective of maternal disease [23–25]. Women requiring azathioprine should have overview in centres experienced in their management.	Likely compatible, data suggest negligible levels in milk [26].
Cyclosporine	Safe	Safe	Safe	There is currently no evidence of teratogenicity, although gestational diabetes can occur [27]. Current guidance advises continuation during pregnancy where required [28].	Likely compatible. There are very little data, although not contraindicated; babies should be monitored, including measurement of levels in infants if there are concerns.
Tacrolimus	Safe	Safe	Safe	There is currently no evidence of teratogenicity, although gestational diabetes can occur. Current guidance advises continuation during pregnancy where required [28].	Likely compatible. Negligible transfer into breast milk reported. Babies should be monitored if clinically indicated [29].
Mycophenolate	Avoid	Avoid	Avoid	Transplacental transfer of mycophenolic acid (the active form of mycophenolate mofetil) occurs, with foetal plasma level reaching levels similar to those of the mother [30], and is classified as a teratogen. High rates of miscarriage and abnormalities have been reported; therefore, effective contraception must be used before and during treatment. Usually, a change to azathioprine is suggested.	Contraindicated, excretion into breast milk is likely. No studies in human lactation
Sirolimus/Everolimus	Avoid	Avoid	Avoid	Animal studies suggest transplacental transfer and foetal toxicity. Human reports indicate a high level of miscarriage with mTOR inhibitors [31]	Contraindicated, animal data show excretion into milk. No human studies
Rituximab	Unclear (limited data available)	Unclear (limited data available)	Unclear (limited data available)	Advice for patients on rituximab is to avoid use at least 6 months before conception. There are little data on exposure to rituximab during pregnancy, with no reports of teratogenicity and some reports of neonatal B cell depletion if used in the second or third trimester [30]. If indicated for severe disease, aim to give dose before or in the early stage [32].	Contraindicated due to lack of data, but not as likely to pass into breast milk as Ig A.

(*continued on next page*)

Table 2 (*continued*)

Drug	First trimester	Second trimester	Third trimester	Pregnancy Comments	Breastfeeding
Belatacept	Avoid	Avoid	Avoid	There are no data on belatacept in human pregnancy. Manufacturer advises avoid pregnancy for at least eight weeks after last injection.	Contraindicated due to lack of data, but not as likely to pass into breast milk as Ig A.
Eculizumab	Avoid	Avoid	Avoid	Case reports of eculizumab usage in anti-phospholipid syndrome or paroxysmal nocturnal haemoglobinuria [33] are reassuring, and treatment for atypical haemolytic uraemic syndrome may be life-saving, although dose or frequency adjustment may be required [34].	Contraindicated due to lack of data, but not as likely to pass into breast milk as Ig A.
Leflunomide	Avoid	Avoid	Avoid	There is no evidence that leflunomide is a human teratogen, although its animal teratogenicity has contraindicated its use in pregnancy. Any woman who wishes to become pregnant or inadvertently becomes pregnant whilst taking leflunomide must undergo a rapid elimination procedure.	Contraindicated due to lack of data
Cyclophosphamide	Avoid	Avoid	Avoid	Placental transfer. Teratogenic. Congenital abnormalities of the skull, ear, face, limb and visceral organs. Increased risk of miscarriage [24,25].	Excreted in breast milk. Discontinue breastfeeding during and for 36 h after treatment.
Hydroxychloroquine	Safe	Safe	Safe	Withdrawal may precipitate lupus flare. Indicated throughout pregnancy if patient has a history of lupus nephritis. Placental transfer. No increase in miscarriage or congenital abnormality. May reduce risk of congenital heart block if maternal anti-SSA and/or anti-SSB antibodies are present [35–40].	Safe

Table 3
Other commonly used drugs including those for renal anaemia.

Drug	First Trimester	Second Trimester	Third Trimester	Pregnancy Comments	Breastfeeding
Aspirin	Safe	Safe		No association with congenital abnormalities. Decreases risk of pre-eclampsia in general obstetric population and in women with CKD. No evidence of maternal haemorrhagic complications [41,42].	Safe
Intravenous Iron	Limited Data	Safe	Safe	Safety data available for the second and third trimesters but limited data on exposure during the first trimester. Expert consensus is not to withhold IV iron if indicated in the first trimester [43–47].	Safe
Low-molecular-weight heparin	Safe	Safe	Safe	No placental transfer. May be needed if proteinuria is high and considered likely to contribute to high thrombotic risk [48].	Safe.
Erythropoietin and Erythropoietin-Stimulating Agents	Limited data but likely safe	Limited data but likely safe	Limited data but likely safe	No placental transfer. Monitor for hypertension [49–51].	Safe
Metformin	Safe	Safe	Safe	Not to be used if pre-pregnancy eGFR <30 ml/min/1.73 m^2 and caution in women with deteriorating renal function in pregnancy [52].	Levels in milk are low, infants receive <0.5% of maternal weight-adjusted dosage. No reported adverse effects

- Avoid all non-essential drugs in the first trimester if possible
- The lowest effective dose should be prescribed (drug-level monitoring wherever possible/relevant) for the shortest period possible
- Drugs that have been extensively used in pregnancy and appear to be usually safe should be used in preference to new or untried drugs
- Drug interactions, e.g. macrolides, with immunosuppressants
- Contribute to the registry evidence base wherever possible

When considering medication choices in breastfeeding mothers, the following considerations should be made:

- The amount of active drug or metabolite delivered to the infant
- Pharmacokinetics of the infant: premature infants or those with organ impairment are at higher risk of adverse events
- Avoid drugs with long half-lives
- Consider timing of doses to avoid peak milk levels
- Use the lowest possible doses and avoid extended treatment courses

Whilst researching detailed summary data, valuable resources such as the British National Formulary, UK Teratology Information Service (UKTIS) found at www.uktis.org and www.toxbase.org can be used. The UKTIS also has a patient-facing website called 'BUMPS', which can be found at www.medicinesinpregnancy.org.

Table 4
Antibiotic safety in pregnancy.

Antibiotic	First trimester	Second trimester	Third trimester	Pregnancy Comments	Breastfeeding
Penicillins	Safe	Safe	Safe	The quality of data pertaining to individual agents varies. It is suggested to refer to data on individual monographs.	Compatible. Possibility of oral candidal infection and gastrointestinal (GI) disturbances due to alteration of oral and GI flora
Amoxicillin	Safe	Safe	Safe	Amoxicillin is an aminopenicillin (structural analogue of penicillin). Many studies have been conducted but have not shown any change in the rate of malformation compared to that of controls. Contrary to the multitude of previously published studies, a study conducted in 2012 found an increased rate of cleft palate with amoxicillin exposure in the first trimester. This requires confirmation to prove a causation and does not alter the view that amoxicillin is safe to use in pregnancy.	Compatible. Peak milk levels occur 4–5 h post dose Possibility of oral candidal infection and gastrointestinal (GI) disturbances due to alteration of oral and GI flora [53]
Phenoxymethylpenicillin (Penicillin V)	Safe	Safe	Safe	There were no reports of adverse outcomes. However, of note is that clearance of penicillin V may be increased during the second and third trimesters	Compatible. Possibility of oral candida and gastrointestinal (GI) disturbances due to alteration of oral and GI flora
Co-amoxiclav	Probably safe	Probably safe	Avoid after 36 weeks	Initial concerns were raised following the ORACLE study [54] and confirmed in a Cochrane review in 2013, in which 22 randomised controlled trials of different antibiotics involving 6872 infants were analysed [55]. Co-amoxiclav was found to be associated with an increased risk of neonatal necrotising enterocolitis (risk ratio 4.72). However, the increased risk was not seen with intact membranes and was associated with co-amoxiclav administered at the time of delivery [56].	Co-amoxiclav is considered compatible with breastfeeding, although the infant should be monitored for any signs of gastrointestinal adverse events. Peak levels occur 4–5 h post dose. Prospective data from 67 women exposed to co-amoxiclav during lactation found that 22% of infants had adverse events, as reported by mothers, which increased with dosage [57]. No pattern was seen, and they were considered minor and self-limiting.
Nitrofurantoin	Can use	Can use	Do not use beyond week 38 or near term	A meta-analysis of nitrofurantoin exposures in the first trimester reported that it was safe in pregnancy [58]. However, an increased risk of haemolytic anaemia occurs in newborns, including those who are glucose-6-phosphate dehydrogenase (G6PD) deficient, if nitrofurantoin is administered close to delivery [53]. Therefore, as a precaution, nitrofurantoin should not be used beyond week 38 or if labour is imminent [59]. A large case-control study in 22,000 women reported that	Studies have found that nitrofurantoin is excreted in breast milk, and although the amounts are considered low, adverse events may be experienced by infants younger than 1 year or in those with G6PD deficiency [10].

				clinical doses (<400 mg per day) were not teratogenic, but neural tube defects and clubfoot occurred at a higher rate in mothers exposed to nitrofurantoin [60]. The MHRA advises that nitrofurantoin may be considered with caution in patients with eGFR between 30 and 44 ml/min/1.73 m^2 for no more than 3–7 days if there are multidrug-resistant organisms that require treatment. Of interest is that high doses (in the region of 10 mg/kg/d) appear to produce transient reductions in spermatogenesis in males, although this effect does not occur in usual clinical doses [53].	
Trimethoprim	Avoid	Use with caution	Use with caution	Trimethoprim is a folate antagonist that crosses the placenta, and Scottish Intercollegiate Guidelines Network (SIGN) on treatment of UTIs in pregnancy (SIGN 88) advises that this drug should not be used for pregnant women with established folate deficiency and low dietary folate intake or women taking other folate antagonists such as anti-epileptics [61]. The benefits of folate supplementation early in pregnancy reduce the risk of cardiac defects and neural tube defects [62] The UK Teratology Information Service recommends that any mother who has had exposure to trimethoprim in the first trimester should receive high-dose folate supplementation [63] at a dose of 5 mg daily until week 12 of pregnancy.	There have been reports of milk concentrations of 1.2–5.5 mcg/mL in mothers taking up to 640 mg trimethoprim daily, with an average milk:plasma ratio of 1.26 and peak levels occurring at 2–3 h [64–66]. These studies were conducted with trimethoprim-sulphamethoxazole, with no adverse effects noted in the nursing infants.
Ciprofloxacin	Not recommended	Use with caution	Use with caution	In humans, it crosses the placenta. There have been a number of reports of ciprofloxacin use that do not seem to demonstrate a pattern of abnormalities, although it may be prudent to avoid use, especially in the first trimester. Inadvertent exposure is not an indication for termination [67]. There have been a few studies looking at quinolones, and in particular ciprofloxacin. These studies have not found increased rates of malformations or birth defects. General consensus is to avoid in pregnancy, as safer alternatives are available [53,68]	Ciprofloxacin is excreted in breast milk, with the milk:serum ratio varying from 0.85 to 2.14 following an oral dose of 750 mg, which peaked at 4 h postdose [53]. There have been a number of reports of ciprofloxacin being used safely in breastfeeding. However, there is an isolated report of pseudomembranous colitis in an infant whose mother self-administered ciprofloxacin (dose unknown) [69] and several reports of green staining of infants' teeth on eruption [70].

(*continued on next page*)

Table 4 (*continued*)

Antibiotic	First trimester	Second trimester	Third trimester	Pregnancy Comments	Breastfeeding
Meropenem and ertapenem	Use with caution	Use with caution	Use with caution	There is a lack of data on the use of carbapenems in pregnancy. There are case reports on the uneventful delivery of two women treated with meropenem at doses of 3 g daily (in divided doses). No abnormalities were reported [71,72]. The UK Teratology Information Service reported data of 6 cases of pregnancies exposed to meropenem, with major congenital malformations rates no higher than background rates. Lack of data indicates that they should be used with a degree of caution [53].	There are very little data, although likely to be similar to other beta-lactams
Cephalosporins	Safe	Safe	Safe	There are some data to suggest an association with congenital malformation and spontaneous abortion, but general consensus is that this class of drugs is generally safe in pregnancy [53,73]	Compatible. Possibility of oral candidal infection and gastrointestinal (GI) disturbances due to alteration of oral and GI flora
Cefalexin	Safe	Safe	Safe	Since the early 1970s, a number of studies have found no association between cephalexin and abnormalities. However, a surveillance study in Medicaid recipients between 1985 and 1992 in 3613 newborns exposed to the drug in the first trimester found an increased rate of cardiovascular and other malformations. Patterns were similar to those seen for another cephalosporin agent, cefaclor [53].	Compatible. Peak milk levels occur at 4 −5 h post dose. Possibility of oral candidal infection and gastrointestinal (GI) disturbances due to alteration of oral and GI flora [74]
Macrolides	Probably safe	Probably safe	Probably safe	The majority of studies reporting in utero exposure to erythromycin do not suggest increased malformations. Erythromycin is the preferred agent if indicated. For further information, see data on individual monographs.	Compatible. Possibility of oral candidal infection and gastrointestinal (GI) disturbances due to alteration of oral and GI flora
Erythromycin	Probably Safe	Probably Safe	Use with caution	Most reports have not found any association between erythromycin use and congenital malformations or spontaneous abortions However, one cohort study found that macrolides were associated with an increased risk of epilepsy or cerebral palsy compared to penicillin, with a hazard ratio of 1.78 [75], but inadvertent exposure should not cause substantial concern [76]	Compatible. Possibility of oral candidal infection and gastrointestinal (GI) disturbances due to alteration of oral and GI flora. Milk:plasma ratio was 0.5 [77]

Clarithromycin	Probably safe	Probably safe	Use with caution	Clarithromycin is widely accepted as safe in pregnancy. There have been over 3000 exposure cases studied, and there is no evidence of an increased risk of malformations (including first-trimester exposures) [53,78]. However, there have been studies that link clarithromycin to an increased risk of spontaneous abortion [79,80] However, not all effects have been studied in sufficient numbers to rule out causation.	Although clarithromycin is widely accepted as compatible with breastfeeding [53], there have been reports of infantile hypertrophic pyloric stenosis with maternal use during the first 14 days post-partum, with infant exposure 2% of mother's dose [81].
Moxifloxacin	Not recommended	Not recommended	Not recommended	There are very few reports of moxifloxacin use in human pregnancy. While not statistically significant, there have been noteworthy trends for increases in congenital malformations with moxifloxacin exposure [82]. Following a single oral dose of 400 mg in 10 women before amniocentesis, approximately 8% of the maternal blood concentration of the drug was seen in amniotic fluid. There were no outcome data from this study [83].	There are no human studies. Although theoretically compatible, breastfeeding is not recommended if safer alternatives are available.
Doxycycline	Use with caution	Not recommended	Not recommended	Doxycycline is a member of the tetracycline family. Much has been documented on the effects of tetracyclines in pregnancy, including adverse effects on teeth, bone and congenital malformations, especially if taken in the second and third trimesters. A Hungarian case–control survey study reported doxycycline-related malformations. The study was not comprehensive and excluded a history of alcohol and tobacco but found rates of congenital abnormality rates in exposed infants similar to controls [84]. These findings have also been demonstrated in studies conducted of doxycycline exposure in the first trimester [85,86]. Further research is required to confirm doxycycline as a safer agent than tetracycline in pregnancy.	Doxycycline is excreted into breast milk with milk:plasma ratios of 0.3–0.4 after 24 h of receiving a dose [87]. Current guidance suggests use of short-term treatment only if necessary [88].

Prescribing issues specific to patients with CKD

During early pregnancy in patients with CKD, glomerular filtration increases significantly above baseline [3]. It is worth noting that the normal calculations of glomerular filtration (e.g. Cockroft-Gault and eGFR) are not valid during pregnancy [4]. There are also changes in proteinuria with associated reductions in serum albumin that alter the handling of drugs that are highly protein bound, and care should be taken to interpret biochemical assays if they do not consider the free:bound ratio. A high urea level may also cause displacement of drugs from their protein-binding sites, further increasing the unbound fraction and potentially increasing risks of adverse events. Commonly used drugs in pregnant women with CKD, such as anti-hypertensives, immunosuppressants, other commonly used drugs including those for renal anaemia and antibiotics are listed in Tables 1–4, respectively.

Summary

Care must be taken when prescribing drugs for women with CKD who are planning to become pregnant or have become pregnant following renal transplantation with consideration of drug safety in each trimester. Good-quality, reliable information can be found in the British National Formulary and Briggs' Drugs in Pregnancy and Lactation [53] and UKTIS resources for patients (BUMPS) and healthcare professionals (TOXBASE).

Practice points

- Patients with renal disease who are planning to become pregnant should be offered pre-pregnancy counselling to optimise their medication
- Care must be taken when prescribing drugs in pregnancy for women with CKD, especially in the first trimester
- There are many pharmacokinetic changes that occur with pregnancy, and these changes may further be complicated by pre-existing renal disease
- Agents with good evidence for safety in pregnancy should be used as first-line choices.

Research agenda

- There is still incomplete knowledge of the effects of antibiotics in pregnancy, as shown by conflicting results in studies
- More data are required about drug safety with newer agents in pregnancy and breastfeeding, e.g. therapeutic antibodies and calcimimetics
- Long-term effects on offspring exposed to medications during pregnancy require further study

Conflicts of interest

The author has no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bpobgyn.2019.03.006.

References

[1] Joint Formulary Committee. British national formulary. 75th edition. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2018.
[2] Bramham K, Hall M, Nelson-Piercy C. Renal disease in pregnancy. second ed. London: Cambridge; 2018.
[3] Koren G, Pastuszak A, Ito S. Drugs in pregnancy. N Engl J Med 1998;338(16):1128–37.
[4] Wiles KS, Nelson-Piercy C, Bramham K. Reproductive health and pregnancy in women with chronic kidney disease. Nat Rev Nephrol 2018 Mar;14(3):165–84.
[5] Laube G, Kemper M, Schubiger G, Nehau T. Angiotensin-converting enzyme inhibitor fetopathy: long-term outcome. Arch Dis Child Fetal Neonatal Ed 2007 Sep;92(5):F402–3. Epub 2007.
[6] Cooper W, Hernandez-Diaz S, Arbogast P, Dudley J, Dyer S, Gideon P, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med 2006 Jun 8;354(23):2443–51.
[7] Nice FJ, DeEugenio D, DiMino TA, Freeny IC, Rovnack MB, Gromelski JS. Medications and breast-feeding: a guide for pharmacists, pharmacy technicians, and other healthcare professionals Part II. J Pharm Technol 2004;20:85–95.
[8] Hypertension in pregnancy: diagnosis and management [CG107]. August 2010 (Updated Jan 2011).
[9] Butters L, Kennedy S, Rubin PC. Atenolol in essential hypertension in pregnancy. BMJ 1990;301:587–9.
[10] Lip GYH, Beevers M, Churchill D, Shaffer LM, Beevers DG. Effect of atenolol on birth weight. Am J Cardiol 1997;79:1436–8.
[11] Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev 2003. CD002863.
[12] Abalos E, Dudley L, Steyn DW, Henderson-Smart DJ. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev 2018.
[13] Lennestål R, Otterblad Olausson P, Källén B. Maternal use of antihypertensive drugs in early pregnancy and delivery outcome, notably the presence of congenital heart defects in the infants. Eur J Clin Pharmacol 2009;65(6):615–25. Epub 2009 Feb 7.
[14] Weber-Schoendorfer C, Hannemann D, Meisterr R, Elefant E, Cupper-Maarschalkerweerd B, et al. The safety of calcium channel blockers during pregnancy: a prospective, multicenter, observational study. Reprod Toxicol 2008;26:24–30.
[15] Magee LA, Schick B, Donnenfeld AE, Sage SR, Conover B, Cook L, et al. The safety of calcium channel blockers in human pregnancy: a prospective, multi-center cohort study. Am J Obstet Gynecol 1996;174(3):823–8.
[16] Walters BNJ, Redman CWG. Treatment of severe pregnancy-associated hypertension with the calcium antagonist nifedipine. Br J Obstet Gynaecol 1984;91:330–6.
[17] Constantine G, Beevers DG, Reynolds AL, Luesley DM. Nifedipine as a second line antihypertensive drug in pregnancy. Br J Obstet Gynaecol 1987;94:1136–42.
[18] Churchill D, Rhodes C, Beevers G. Diuretics for preventing pre-eclampsia. Cochrane Database Syst Rev 2007 Jan 24.
[19] De Vetten L, van Stuijvenberg M, Kema IP, Bocca G. Maternal use of prednisolone is unlikely to be associated with neonatal adrenal suppression-a single-center study of 16 cases. Eur J Pediatr 2017;176(8):1131–6.
[20] Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. Am J Med Genet 1999;86:242–4.
[21] Park-Wyllie L, Mazzotta P, Pastuszake S, Moretti M, Beique L, Hunnisett L. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology 2000;62:385–482.
[22] Hviid A, Mølgaard-Nielse D. Corticosteroid use during pregnancy and risk of orofacial clefts. Can Med Assoc J April 19, 2011;183(7):796–804. https://doi.org/10.1503/cmaj.101063. http://www.cmaj.ca/content/183/7/796.
[23] Francella A, Dyan A, Bodian C, Rubin P, Chapman M, Present DH. The safety of 6-mercaptopurine for childbearing patients with inflammatory bowel disease: a retrospective cohort study. Gastroenterology 2003;124:9–17.
[24] Flint J, Panchal S, Hurrell A, van de Venne M, Gayed M, Schreiber K, et al., BSR and BHPR Standards GAAWG. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford) 2016;55:1693–7.
[25] Götestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis 2016;75:795–810.
[26] Sau A, Clarke S, Bass J, Kaiser A, Marinaki A, Nelson-Piercy C. Azathioprine and breastfeeding: is it safe? BJOG 2007;114:498–501.
[27] Chakkera HA, Kudva Y, Kaplan B. Calcineurin inhibitors: pharmacologic mechanisms impacting both insulin resistance and insulin secretion leading to glucose dysregulation and diabetes mellitus. Clin Pharmacol Ther 2017;101:114–20.
[28] European best practice guidelines for renal transplantation. Section IV: long-term management of the transplant recipient. IV.10. Pregnancy in renal transplant recipients. Nephrol Dial Transplant 2002;17(Suppl. 4):50–5.
[29] Bramham K, Chusney G, Lee J, Lightstone L, Nelson-Piercy C. Breastfeeding and tacrolimus: serial monitoring in breast-fed and bottle-fed infants. Clin J Am Soc Nephrol 2013 Apr;8(4):563–7.
[30] Tjeertes IF, Bastiaans DE, van Ganzewinkel CJ, Zegers SH. Neonatal anemia and hydrops fetalis after maternal mycophenolate mofetil use. J Perinatol 2007;27(1):62–4.
[31] Coscia L, Constantinescu S, Moritz M, Frank A, Ramirez C, Doria C. Report from the national transplantation pregnancy registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 2010:65–85. Los Angeles.
[32] De Cock D, Birmingham L, Watson K, Kearsley-Fleetk L, Symmons D, Hyrichk K. Pregnancy outcomes in women with rheumatoid arthritis ever treated with rituximab. Rheumatology 1 April 2017;56(Issue 4):661–3.
[33] Kelly RJ, Höchsmann B, Szer J, Kulasekararaj A, de Guibert S, Röth A, et al. Eculizumab in pregnant patients with paroxysmal nocturnal hemoglobinuria. N Engl J Med 2015;373:1032–9.
[34] Bruel A, Kavanagh D, Noris M, Delmas Y, Wong EKS, Bresin E, et al. Hemolytic uremic syndrome in pregnancy and postpartum. Clin J Am Soc Nephrol 2017.
[35] Moroni G, Doria A, Giglio E, Tani C, Zen M, Strigini F, et al. Fetal outcome and recommendations of pregnancies in lupus nephritis in the 21st century. A prospective multicenter study. J Autoimmun 2016;74:6–12.
[36] Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, Khamashta MA, Kim MY, Saxena A, et al. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. Circulation 2012;126:76–82.

[37] Wallace DJ, Gudsoorkar VS, Weisman MH, Venuturupalli SR. New insights into mechanisms of therapeutic effects of antimalarial agents in SLE. Nat Rev Rheumatol 2012;8:522–33.
[38] Kaplan YC, Ozsarfati J, Nickel C, Koren G. Reproductive outcomes following hydroxychloroquine use for autoimmune diseases: a systematic review and meta-analysis. Br J Clin Pharmacol 2016;81:835–48.
[39] Clowse MEB, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. Arthritis Rheum 2006;54:3640–7.
[40] Marmor MF, Kellner U, Lai TYY, Melles RB, Mieler WF, Ophthalmology AAO. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). Ophthalmology 2016;123:1386–94.
[41] Henderson JT, Whitlock EP, O'Conner E, Senger CA, Thompson JH, Rowland MG. Low-dose aspirin for the prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive services task force. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014.
[42] Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med 2017;377:613–22.
[43] Albaramki J, Hodson EM, Craig JC, Webster AC. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. Cochrane Database Syst Rev 2012;1:CD007857.
[44] Tariq N, Ayub R, Khan WU, Ijaz S, Alam AY. Parenteral iron therapy in the treatment of iron deficiency anemia during pregnancy: a randomized controlled trial. J Coll Phys Surg Pak 2015;25:193–7.
[45] Kriplani A, Mahey R, Dash BB, Kulshreshta V, Agarwal N, Bhatla N. Intravenous iron sucrose therapy for moderate to severe anaemia in pregnancy. Indian J Med Res 2013;138:78–82.
[46] Al RA, Unlubilgin E, Kandemir O, Yalvac S, Cakir L, Haberal A. Intravenous versus oral iron for treatment of anemia in pregnancy: a randomized trial. Obstet Gynecol 2005;106:1335–40.
[47] al-Momen AK, al-Meshari A, al-Nuaim L, Saddique A, Abotalib Z, Khashogji T, et al. Intravenous iron sucrose complex in the treatment of iron deficiency anemia during pregnancy. Eur J Obstet Gynecol Reprod Biol 1996;69:121–4.
[48] Gynaecologists RCOOA. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green-top Guideline 2015;37a.
[49] McMullin MF, White R, Lappin T, Reeves J, MacKenzie G. Haemoglobin during pregnancy: relationship to erythropoietin and haematinic status. Eur J Haematol 2003;71:44–50.
[50] Sienas L, Wong T, Collins R, Smith J. Contemporary uses of erythropoietin in pregnancy: a literature review. Obstet Gynecol Surv 2013;68:594–602.
[51] Sanchez-Gonzalez LR, Castro-Melendez SE, Angeles-Torres AC, Castro-Cortina N, Escobar-Valencia A, Quiroga-Garza A. Efficacy and safety of adjuvant recombinant human erythropoietin and ferrous sulfate as treatment for iron deficiency anemia during the third trimester of pregnancy. Eur J Obstet Gynecol Reprod Biol 2016;205:32–6.
[52] Excellence NIFHAC. Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period. NG3; 2015.
[53] Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation : a reference guide to foetal and neonatal risk. Available from: http://www.medicinescomplete.com/#/content/dpl/Briggs. [Accessed 2 July 2018].
[54] Kenyon S, Taylor DJ, Tarnow-Mordi WO, ORACLE Collaborative Group. ORACLE–antibiotics for preterm prelabour rupture of the membranes: short-term and long-term outcomes. Acta Paediatr Suppl 2002;91(437):12–5.
[55] Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. Cochrane Database Syst Rev 2013;12:CD001058.
[56] Williams M, Spencer R. Caesarean section: summary of updated NICE guidance. BMJ 2011;343:d7108.
[57] Benyamini L, Merlob P, Stahl B, Braunstein R, Bortnik O, Bulkowstein M, et al. The safety of amoxicillin/clavulanic acid and cefuroxime during lactation. Ther Drug Monit 2005;27:499–502.
[58] Ben David S, Einarson T, Ben David Y, Nulman T, Pastuszakd A, Koren G. The safety of nitrofurantoin during the first trimester of pregnancy: meta-analysis. Fundam Clin Pharmacol 1995;9:503–7.
[59] Apgar V. Drugs in pregnancy. J Am Med Assoc 1964;190:840.
[60] Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. Nitrofurantoin and congenital abnormalities. Eur J Obstet Gynecol Reprod Biol 2001;95:119–26.
[61] Scottish Intercollegiate Guidelines Network (SIGN). Management of suspected bacterial urinary tract infections in adults. Edinburgh: SIGN; 2012 (SIGN guidance No. 88) [Online] Available from URL: http://www.sign.ac.uk. Accessed 02/07/2018.
[62] Shepard TH, Brent RL, Friedman JM, Jones KL, Miller RK, Moore CA, et al. Update on new developments in the study of human teratogens. Teratology 2002;65:153–61.
[63] UK Teratology Information Service. Trimethoprim in pregnancy monograph [Online]. Available at: http://www.medicinesinpregnancy.org/Medicine–pregnancy/Trimethoprim/; 2013. Accessed 02/07/2018.
[64] Pagliaro LA, Levin RHPagliaro LA, Levin RH. Problems in pediatric drug therapy. Hamilton, IL: Drug Intell Publications; 1979.
[65] Miller RD, Salter AJMiller RD, Salter AJ. The passage of trimethoprim/sulphamethoxazole into breast milk and its significance. In: Progress in chemotherapy. Athens: Proceedings of the Eighth International Congress of Chemotherapy; 1973. p. 687–91.
[66] Anon, Committee on Drugs & American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. Pediatrics 1994;93:137–50.
[67] Schaefer C, Amoura-Elefant E, Vial T, Ornoy A, Garbis H, Robert E, et al. Pregnancy outcome after prenatal quinolone exposure. Evaluation of a case registry of the European Network of Teratology Information Services (ENTIS). Eur J Obstet Gynecol Reprod Biol 1996;69:83–9.
[68] UK Teratology Information Service. Ciprofloxacin in pregnancy monograph [Online]. Available at: http://www.medicinesinpregnancy.org/Medicine–pregnancy/Ciprofloxacin/; 2017. 02/07/2018.
[69] Harmon T, Burkhart G, Applebaum H. Perforated pseudomembranous colitis in the breast-fed infant. J Pediatr Surg 1992;27:744–6.
[70] Lumbiganon P, Pengsaa K, Sookpranee T. Ciprofloxacin in neonates and its possible effect on the teeth. Pediatr Infect Dis J 1991;10:619–20.

[71] Shea K, Hilburger E, Baroco A, Oldfield E. Successful treatment of vancomycin-resistant Enterococcus faecium pyelonephritis with daptomycin during pregnancy. Ann Pharmacother 2008;42:722–5.
[72] Yoshida M, Matsuda H, Furuya K. Successful prognosis of brain abscess during pregnancy. J Reproduction Infertil 2013;14:152–5.
[73] UK Teratology Information Service. Cephalosporins in pregnancy monograph [Online]. Available at: http://www.medicinesinpregnancy.org/Medicine–pregnancy/Cephalosporins/; 2017. Accessed 02/07/2018.
[74] Ilett KF, Hackett LP, Ingle B, Bretz PJ. Transfer of probenecid and cephalexin into breast milk. Ann Pharmacother 2006;40:986–9.
[75] Meeraus WH, Petersen I, Gilbert R. Association between antibiotic prescribing in pregnancy and cerebral palsy or epilepsy in children born at term: a cohort study using the health improvement network. PLoS One 2015;10(3):e0122034.
[76] UK Teratology Information Service. Macrolides in pregnancy monograph [Online]. Available at: https://www.toxbase.org/Poisons-Index-A-Z/M-Products/Macrolides-in-pregnancy/; 2017. Accessed 02/07/2018.
[77] Ito S, Blajchman A, Stephenson M, Eliopoulos C, Koren G. Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication. Am J Obstet Gynecol 1993;168:1393–9.
[78] Andersen JT, Petersen M, Jimenez-Solem E, Broedbaek K, Andersen N, Torp-Pedersen C, et al. Clarithromycin in early pregnancy and the risk of miscarriage and malformation: a register based nationwide cohort study. PLoS One 2013;8(1):e53327.
[79] Muanda FT, Sheehy O, Berard A. Use of antibiotics during pregnancy and risk of spontaneous abortion. CMAJ (Can Med Assoc J) 2017;189(17):E625–33.
[80] Einarson A, Phillips E, Mawji F, D'Alimonte D, Schick B, Addis A, et al. A prospective controlled multicentre study of clarithromycin in pregnancy. Am J Perinatol 1998;15(9):523–5.
[81] Lund M, Pasternak B, Davidsen R, Feenstra B, Krogh C, Diaz L. Use of macrolides in mother and child and risk of infantile hypertrophic pyloric stenosis: nationwide cohort study. BMJ 2014;348:g1908.
[82] Padberg S, Wacker E, Meister R, Panse M, Weber-Scoendorfer C, Oppermann M, et al. Antimicrob Agents Chemother 2014 Aug;58(8):4392–8.
[83] Ozyuncu O, Beksac MS, Nemutlu E, Katlan D, Kir S. Maternal blood and amniotic fluid levels of moxifloxacin, levofloxacin and cefixime. J Obstet Gynecol 2010;36:484–7.
[84] Czeizel AE, Rockenbauer M. Teratogenic study of doxycycline. Obstet Gynecol 1997;89:524–8.
[85] Cooper W, Hernandez-Diaz S, Arbogast P, Dudley J, Dyer S, Gideon P. Antibiotics potentially used in response to bioterrorism and the risk of major congenital malformations. Paediatr Perinat Epidemiol 2009;23:18–28.
[86] Horne Jr HW, Kundsin RB. The role of mycoplasma among 81 consecutive pregnancies: a prospective study. Int J Fertil 1980;25:315–7.
[87] Morganti G, Ceccarelli G, Ciaffi EG. Comparative concentrations of a tetracycline antibiotic in serum and maternal milk. Antibiotica 1968;6:216–23.
[88] Hale T. Medications and mothers milk. ninth ed. Amarillo, TX: Pharmasoft Publishing; 2000. p. 225–6.