MEDICINES AND BIRTH DEFECTS

Some medicines are known to cause abnormal fetal development resulting in fetal death or babies born with birth defects. Some of these effects may happen very early in pregnancy, within the first 6 weeks of gestation, before most patients realise they are pregnant. It is therefore important that women who are in their reproductive age and are prescribed any teratogenic medicine should be made aware of the risk and placed on reliable contraception. Some medicines can cause fetal damage in the second or third trimester.

Where possible, stop teratogenic medicines before a pregnancy is planned and prescribe suitable alternatives.

Any medicine that is prescribed during pregnancy must be carefully evaluated, and risk versus benefit should be assessed before use. Refer to prescriber information for details regarding risks in pregnancy. .

Refer pregnancies exposed to teratogenic medicines during the first trimester for a detailed fetal anomaly scan.

The table below lists some commonly used medicines that are associated with birth defects.

MEDICINES	ADVERSE FETAL EFFECTS	*LoE*
Androgens	Masculinisation of the developing female fetus can occur.	*III*[i]
ACE- inhibitors/ ARBs	Fetal hypotension resulting in fetal kidney hypoperfusion and anuria, with fetal growth restriction and demise.	*III*[ii]
Anticonvulsants:		
Carbamazepine	Increases the risk of facial dysmorphology, neural tube defects, cardiovascular defects, and urinary tract defects.	*II*[iii]
Phenytoin	Increases the risk of fetal hydantoin syndrome, consisting of facial dysmorphology, cleft palate, ventricular septal defect, and growth and intellectual disability.	
Valproate	Increases the risk of spina bifida, facial dysmorphology, autism, atrial septal defect, cleft palate, hypospadias, polydactyly, craniosynostosis, limb abnormalities, neurodevelopmental problems (approximately 40%) and autism[iv].	

[i] Androgens:Wilkins L. Masculinization of female fetus due to use of orally given progestins. JAMA. 1960 Mar 5;172(10):1028–32. https://jamanetwork.com/journals/jama/article-abstract/327726

[ii] Hanssens M, Keirse MJ, Vankelecom F, Van Assche FA. Fetal and neonatal effects of treatment with angiotensin-converting enzyme inhibitors in pregnancy. Obstet Gynecol. 1991 Jul;78(1):128–35. https://www.ncbi.nlm.nih.gov/pubmed/2047053

[iii] Anticonvulsants: Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, Hounsome J, McKay AJ, Tudur Smith C, Marson AG. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev. 2016 Nov 7;11:CD010224. https://www.ncbi.nlm.nih.gov/pubmed/27819746

[iv] Valproic acid – caution in pregnancy: European Medicines Agency - Pharmacovigilance Risk Assessment Committee. Assessment report EMA/198940/2018 - valproate exposure in pregnancy, 8 February 2018.

Antidepressants	SSRIs should in general be continued during pregnancy and breastfeeding. There is uncertainty in the evidence, but potential complications may include an increased risk of birth defects, postpartum haemorrhage, premature birth and low birth weight.	*III*[v]
Carbimazole	Increased risk of birth defects in the first trimester and at high daily doses of ≥15 mg.	*III*[vi]
Dolutegravir	There is an increased risk of neural tube birth defects involving the brain, spine, and spinal cord; if used within the first 6 weeks of pregnancy.	*III*[vii]
Efavirenz	No increased prevalence of birth defects detected and in a large multi-cohort analysis or from a South African exposure registry.	*I*[viii]
Lithium	First trimester exposure is associated with an increased risk of birth defects.	*II*[ix]
Macrolide	In a large population-based cohort study, when compared to penicillin, first trimester macrolide exposure was associated with increased risk of cardiovascular malformations, and macrolide exposure in any trimester was associated with increased risk of genital malformations. The majority of macrolide exposures in	*III*[x]

http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Valproate_2017_31/Position_provided_by_CMDh/WC500250221.pdf

Valproic acid – caution in pregnancy: Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008 Sep;81(1):1-13. https://www.ncbi.nlm.nih.gov/pubmed/18565732

[v] Antidepressants: ACOG Committee on Practice Bulletins--Obstetrics. ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces practice bulletin number 87, November 2007). Use of psychiatric medications during pregnancy and lactation. Obstet Gynecol. 2008 Apr;111(4):1001–20. https://www.ncbi.nlm.nih.gov/pubmed/18378767

Antidepressants: National Institute of Clinical Excellence: National Clinical Guideline Number 192: Antenatal and postnatal mental health – clinical management and service guidance, April 2018. https://www.nice.org.uk/guidance/cg192/evidence/full-guideline-pdf-4840896925

[vi] Carbimazole: Bowman P, Vaidya B. Suspected Spontaneous Reports of Birth Defects in the UK Associated with the Use of Carbimazole and Propylthiouracil in Pregnancy. J Thyroid Res. 2011;2011:235130. https://www.ncbi.nlm.nih.gov/pubmed/21922050

[vii] Dolutegravir: Raesima MM, Ogbuabo CM, Thomas V, Forhan SE, Gokatweng G, Dintwa E, et al. Dolutegravir Use at Conception - Additional Surveillance Data from Botswana. N Engl J Med. 2019 29;381(9):885–7. https://www.ncbi.nlm.nih.gov/pubmed/31329378

[viii] Efavirenz: Mehta UC, van Schalkwyk C, Naidoo P, Ramkissoon A, Mhlongo O, Maharaj NR, et al. Birth outcomes following antiretroviral exposure during pregnancy: Initial results from a pregnancy exposure registry in South Africa. South Afr J HIV Med. 2019;20(1):971. https://www.ncbi.nlm.nih.gov/pubmed/31616571

Efavirenz: Martinez de Tejada B, European Pregnancy and Paediatric HIV Cohort Collaboration Study Group. Birth Defects After Exposure to Efavirenz-Based Antiretroviral Therapy at Conception/First Trimester of Pregnancy: A Multicohort Analysis. J Acquir Immune Defic Syndr. 2019 01;80(3):316–24. https://www.ncbi.nlm.nih.gov/pubmed/30570524

Efavirenz: Zash R, Holmes L, Diseko M, Jacobson DL, Brummel S, Mayondi G, Isaacson A, Davey S, Mabuta J, Mmalane M, Gaolathe T, Essex M, Lockman S, Makhema J, Shapiro RL. Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana. N Engl J Med. 2019 Aug 29;381(9):827-840. https://www.ncbi.nlm.nih.gov/pubmed/31329379

[ix] Lithium: Munk-Olsen T, Liu X, Viktorin A, Brown HK, Di Florio A, D'Onofrio BM, et al. Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies. Lancet Psychiatry. 2018 Aug;5(8):644-652. https://www.ncbi.nlm.nih.gov/pubmed/29929874

[x] Fan H, Gilbert R, O'Callaghan F, Li L. Associations between macrolide antibiotics prescribing during pregnancy and adverse child outcomes in the UK: population based cohort study. BMJ. 2020 Feb 19;368:m331. https://www.ncbi.nlm.nih.gov/pubmed/32075790

	this study (93%) were to erythromycin, but a class effect cannot be ruled out. Macrolides should only be prescribed in pregnancy when clearly indicated.	
Methotrexate	Pregnancy loss, growth restriction, microcephaly, intellectual disability.	*III*[xi]
Contraceptive agents and sex steroids (progestin)	There is no risk for congenital defects if contraceptive agents were used inadvertently during the first trimester. Very high doses of androgen hormone-derived progestin may produce masculinisation if used before 13 weeks of pregnancy.	*II*[xii]
Prednisone	Prednisone does not represent a major teratogenic risk in humans at therapeutic doses, but there is an increased risk (about 3-fold) for cleft palate.	*II*[xiii]
Retinoids	Oral formulation is associated with increased risk of CNS, cardioaortic, ear, and clefting defects. Topical administration is very unlikely to have teratogenic potential because teratogenic serum levels cannot be attained by topical exposure to retinoids.	*III*[xiv]
Tetracyclines (e.g. docycycline)	Produces bone and teeth staining; it does not increase the risk of any malformations but should not be used during pregnancy.	*III*[xv]
Warfarin	Early exposure during pregnancy can result in nasal hypoplasia, intrauterine growth restriction and miscarriage. CNS malformations can occur in late pregnancy exposure because of bleeding. In women with new generation prosthetic heart valves taking warfarin daily at a dose of ≤5mg, the risk of serious teratogenesis is small and warfarin may be safely continued in the first trimester being discontinued prior to delivery to avoid intracranial bleeding in the newborn (substituted with heparin).	*II*[xvi]

ACE-inhibitor: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; LoE: level of evidence; DS-TB: drug-sensitive tuberculosis; RHZE: rifampicin/isoniazid/pyrazinamide/ethambutol; CNS: central nervous system

[xi] Methotrexate: Kozlowski RD, Steinbrunner JV, MacKenzie AH, Clough JD, Wilke WS, Segal AM. Outcome of first-trimester exposure to low-dose methotrexate in eight patients with rheumatic disease. Am J Med. 1990 Jun;88(6):589–92. https://www.ncbi.nlm.nih.gov/pubmed/2189302

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[xvi] Warfarin: Steinberg ZL, Dominguez-Islas CP, Otto CM, Stout KK, Krieger EV. Maternal and Fetal Outcomes of Anticoagulation in Pregnant Women With Mechanical Heart Valves. J Am Coll Cardiol. 2017 Jun 6;69(22):2681–91. https://www.ncbi.nlm.nih.gov/pubmed/28571631