Medicines with teratogenic potential: what is effective contraception and how often is pregnancy testing needed? Guidance for primary care clinicians

Some medicines are known or suspected to have the potential to increase the risk of birth defects and development disorders (teratogenic potential) when taken during pregnancy, especially during the first trimester (up to week 12 of pregnancy), when a woman may not know she is pregnant. The product information for these medicines advise that pregnancy should be avoided during treatment, with advice on the need to use contraception including, in some cases, formal pregnancy prevention programmes.

When using any medicine with teratogenic potential, a woman should be advised of the risks and encouraged to use the most effective contraceptive method taking into account her personal circumstances.

In March 2019 the MHRA released a drug safety update providing new guidance on contraceptive methods and frequency of pregnancy testing to reduce inadvertent exposures during pregnancy in a woman taking a medicine of teratogenic potential. They provide a useful aide-memoire table for prescribers, produced by The Medicines for Women's Health Expert Advisory Group of the Commission on Human Medicines.

The Faculty of Sexual and Reproductive Health (FSRH) provides guidance on 'Contraception for women using known teratogenic drugs or drugs with potential teratogenic effects'. Interactions with hormonal contraception must be considered when choosing the most appropriate contraceptive method – see FSRH Drug Interactions with Hormonal Contraception.

There is no nationally produced list of medicines with teratogenic potential.

Below are two tables containing information on the teratogenicity of key drugs. **This is not a comprehensive list**. Teratogenic information from TOXBASE®[1] has been reviewed, where available, as well as information in the BNF and individual drug Summaries of Product Characteristics (SPCs). Where it is considered that the risk of teratogenicity in the first few weeks of pregnancy is high, and therefore the need for pregnancy testing before the issue of repeat prescriptions may be justified, they have been included in the tables. **However, the risks/benefits of all drugs should be reviewed if pregnancy occurs during treatment or conception is planned.**

Table 1 provides information on drugs that are commonly prescribed in primary care. Consideration should be given to implementing processes that enable the recommendations for pregnancy testing, as specified in the aide-memoire table, to be taken into account before any repeat prescription for the listed drug is issued.

Table 2 contains drugs that are rarely prescribed in primary care, such as thalidomide, but which have been listed due to their known potent teratogenicity.

[1] TOXBASE® is a product of the UK National Poisons Information Service. It provides systematic evidence based reviews on maternal exposures to various drugs and chemicals provided by the UK Teratology Information Service (UKTIS). UKTIS is a national service commissioned by Public Health England which is the sole dedicated UK provider of evidence-based information on fetal risk. Registration with TOXBASE® is required for NHS users and accounts are issued per unit/practice.

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Table 1 – Medicines commonly prescribed in primary care

Medication	Evidence of teratogenicity	Details of teratogenicity
Antiepileptic drugs (AEDs)	MHRA BNF	There is an increased risk of teratogenicity associated with the use of AEDs (especially if used during the first trimester and particularly if the patient is taking two or more AEDs). Valproate, in particular, is highly teratogenic – see individual entry for more information. In the context of the known harms with valproate, the Commission on Human Medicines (CHM) has reviewed available safety data relating to the use of other key antiepileptic drugs in pregnancy. For carbamazepine, phenobarbital, phenytoin, and topiramate, the data showed that use during pregnancy was associated with an increased risk of major congenital malformations; the risk for carbamazepine, phenobarbital, and topiramate was shown to be dose dependent. There is the possibility of adverse effects on neurodevelopment associated with the use of phenobarbital, topiramate and phenytoin, and an increased risk of intra-uterine growth restriction with phenobarbital, topiramate, and zonisamide. See individual entries for carbamazepine, phenytoin, topiramate and valproate for more information. Female patients should be advised not to stop their antiepileptic treatment without discussing this with their doctor, and to seek urgent medical advice if they are on AEDs and think they could be pregnant.
Carbamazepine	MHRA TOXBASE® BNF	Carbamazepine use in pregnancy has been associated with an increased risk of major congenital malformations. Evidence suggests that the risk of malformation with carbamazepine may be dose dependent. Carbamazepine reduces the efficacy of hormonal contraception. Acceptable forms of contraception include an intrauterine method (Cu-ICD or LNG-IUS), or the medroxyprogesterone acetate depot injection PLUS a barrier method.
Carbimazole	MHRA TOXBASE® BNF	Carbimazole is associated with an increased risk of congenital malformations, especially when administered in the first trimester of pregnancy and at high doses (15 mg or more of carbimazole daily).
Colchicine	BNF SPC	Avoid—teratogenicity in animal studies. The SPC states: *Colchicine is genotoxic in vitro and in vivo, and is teratogenic in animal studies. Colchicine is therefore contraindicated in pregnancy. Women of childbearing potential have to use effective contraception during treatment.*
GnRH analogues	BNF SPC	Use of GnRH agonists during pregnancy is associated with a theoretical risk of abortion or foetal abnormality. Prior to treatment, potentially fertile women should be examined to exclude pregnancy. Non-hormonal methods of contraception should be employed during therapy until menses resume following discontinuation of treatment. Note – this advice differs from information in the aide-memoire table referenced above.
Leflunomide	TOXBASE® BNF	Leflunomide is teratogenic in animal models and is therefore generally contraindicated in human pregnancy. Limited human data do not suggest an increased risk of adverse pregnancy outcomes (including congenital malformation) where exposure to the drug is ceased upon recognition of pregnancy and a washout protocol is implemented. However, one case-control study described a non-statistically significant association between infant cardiovascular malformation and use of leflunomide without washout therapy in the first trimester.
Methotrexate	TOXBASE® BNF	The available data demonstrate that high dose methotrexate used in medical termination and the treatment of ectopic pregnancy is a teratogen that causes a distinct embryopathy. Data on lower doses of methotrexate are too limited to permit a risk assessment of teratogenic potential.
Modafinil	MHRA/CHM BNF SPC	Post-marketing reports show that the use of modafinil in pregnancy is suspected to cause congenital malformations such as congenital heart defects, hypospadias, and orofacial clefts.
Mycophenolate	MHRA TOXBASE® BNF	Mycophenolate mofetil is a confirmed teratogen and human data indicates an increased risk of congenital malformations following exposure during pregnancy. It is also known to increase the risk of first trimester pregnancy loss.

Phenytoin	MHRA SPC	Phenytoin use in pregnancy has been associated with an increased risk of major congenital malformations. There is the possibility of adverse effects on neurodevelopment. Phenytoin reduces the efficacy of hormonal contraception. Acceptable forms of contraception include an intrauterine method (Cu-ICD or LNG-IUS), or the medroxyprogesterone acetate depot injection PLUS a barrier method.
Statins	TOXBASE® BNF SPC	The available data do not support an association between in utero exposure to statins and any of the adverse pregnancy outcomes that have been studied, with the possible exception of preterm delivery and spontaneous pregnancy loss. However, some important pregnancy outcomes such as offspring neurodevelopment, a key feature of some cholesterol synthesis disorders, have not been studied and the data are thus insufficient to exclude an increased risk. Current guidelines on diseases in which statins are frequently prescribed recommend that women wishing to become pregnant stop use of statins three months prior to attempting to conceive, or as soon as pregnancy is confirmed. The SPCs of all statins contraindicate use in pregnancy
Topiramate	MHRA TOXBASE® BNF	**Topiramate is contraindicated in pregnancy and in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled.** Use during pregnancy has been associated with an increased risk of major congenital malformation, neurodevelopmental disorders and fetal growth restriction. The risk has been reported to be dose dependent; effects were observed in all doses. Topiramate can potentially reduce the efficacy of hormonal contraception. Acceptable forms of contraception include an intrauterine method (Cu-ICD or LNG-IUS), or the medroxyprogesterone acetate depot injection PLUS a barrier method.
Trimethoprim	TOXBASE® BNF	Trimethoprim use during the first trimester may increase the risk of certain congenital malformations due to folate antagonistic effects.
Valproate	MHRA TOXBASE® BNF	**Valproate is contraindicated in female patients aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the Pregnancy Prevention Programme are fulfilled.** The risk of congenital malformation following first trimester valproate exposure is estimated as being 2- to 5-fold higher than that in unexposed pregnancies. Sodium valproate exposure in utero is also associated with adverse neurodevelopmental outcomes in the offspring including effects on IQ, language development, and increased rates of autistic spectrum disorder.
Warfarin	TOXBASE® BNF	Fetal warfarin syndrome (FWS) is a well-recognised complication following warfarin exposure in pregnancy. The critical period for the development of FWS has not been precisely defined, although data suggests that the risk period covers gestational weeks 6-12. Use of warfarin in early pregnancy may be associated with an increased incidence of spontaneous abortion and other congenital malformations not typically associated with FWS.

Table 2 – Medicines with known potent teratogenicity prescribed in secondary care

Medication	**Evidence of teratogenicity**	**Details of teratogenicity**
Antiretrovirals (Dolutegravir)	MHRA TOXBASE® BNF	All treatment options require careful assessment by a specialist. An MHRA alert highlights that use of dolutegravir around the time of conception may cause neural tube defects in the infant. Women of childbearing potential should be counselled about the potential risk, including consideration of effective contraceptive measures.
Fingolimod	MHRA BNF	Fingolimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Exposure in pregnancy is thought to lead to an estimated additional 2–3 cases of major congenital malformation per 100 livebirths compared with the general population (a two-fold increase)
Oral retinoids	MHRA TOXBASE® BNF	**Oral retinoids are strictly contraindicated in women of childbearing potential, unless all conditions in a Pregnancy Prevention Programme (PPP) are fulfilled, and every oral retinoid has a dedicated and specific PPP.** The risk of foetal malformation with oral retinoids is extremely high, even when used at a low dose or for a short time during pregnancy. Note: Systemic exposure is thought to be negligible following application of topical retinoids during pregnancy. However, since risk cannot be excluded, use of topical retinoids is contraindicated during pregnancy as a precaution. Women and girls should be

		advised not to use topical retinoids if they are planning a pregnancy and to use effective contraception to minimise the risk of accidental exposure in pregnancy if they are of childbearing potential.
Thalidomide and its analogues (lenalidomide and pomalidomide)	TOXBASE® BNF	Thalidomide is a powerful human teratogen, inducing a high frequency of severe and life-threatening birth defects. Thalidomide must never be used by women who are pregnant or by women who could become pregnant unless all the conditions of the Pregnancy Prevention Programme are met. The conditions of the Pregnancy Prevention Programme must be fulfilled for all male and female patients. Lenalidomide and pomalidomide are structurally related to thalidomide. They have found to be teratogenic in animals, and so if taken during pregnancy, a teratogenic effect in humans is expected. The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.
Tolvaptan	BNF SPC	Tolvaptan is contraindicated in pregnancy. There are no or limited amount of data from the use of tolvaptan in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Version history

Version number	Date	Details of change
V1	November 2019	New guideline document
V2	July 2020	Modafinil – added as a new entry to Table 1 following a letter to prescribers from the British Generic Manufacturers Association, in agreement with the MHRA stating, based on recent data, the overall rate of major congenital malformations was approximately 15% for women taking modafinil, compared to 3% in the general population.
V3	September 2020	Tolvatan (Jinarc) – added as anew entry to Table 2 due to newly published manufacturers risk materials
V4	August 2021	Antiepileptic drugs – information changed to incorporate the MHRA alert Antiepileptic drugs in pregnancy: updated advice following comprehensive safety review GnRH analogues – added as a new entry to Table 1 following work to develop a SCP for endometriosis. Antiretrovirals – entry edited to remove the C/I of use in pregnancy following MHRA alert Dolutegravir (Tivicay▼, Triumeq▼, Juluca▼): updated advice on increased risk of neural tube defects All references to Jinarc removed from tolvaptan entry as contraindication applies to all tolvaptan products.
V5	April 2023	Topiramate and Antiepileptic drugs section - information changed to incorporate the MHRA alert Topiramate (Topamax): start of safety review triggered by a study reporting an increased risk of neurodevelopmental disabilities in children with prenatal exposure. Carbamazepine information edited to incorporate guidance from 'Antiepileptic drugs in pregnancy: updated advice following comprehensive safety review.
V6	August 2024	Valproate guidance updated. Information about topiramate PPP added. Individual entry for phenytoin added. Links updated