DRUGS IN PREGNANCY

A MOTHERSAFE Approach

What Doctors Should Know

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NSW State-wide free telephone

Exposures in Pregnancy and Lactation Advisory service

at the Royal Hospital for Women

- Specialised service funded by the Ministry of Health. Established in 2000.
- Directed by Dr Debra Kennedy; Geneticist and Paediatrician with established expertise in Clinical Teratology.
- Telephone counselling:

  Hours: Monday-Friday 9am – 5pm

  (excluding public holidays)

(02) 93826539 (Sydney Metropolitan Area)

1800647848 (Non-Metropolitan Area)

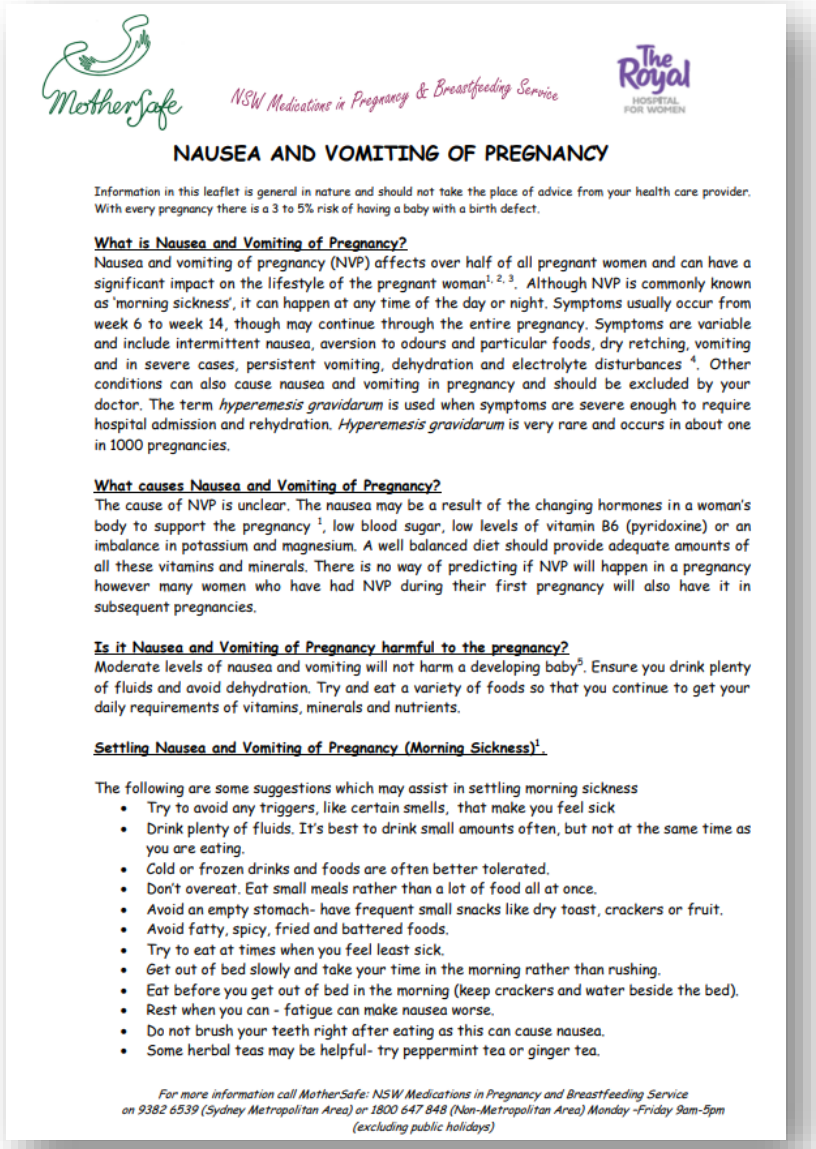
ROLE OF MOTHERSAFE

- To provide evidence based information and advice to various HCPs (GPs; Obstetricians; Lactation Consultants; Early Childhood Nurses; Pharmacists etc.), as well as consumers regarding ANY exposure in pregnancy or breastfeeding.

  - Medicines (prescription, OTC medicines, complementary)
  - Illicit substances
  - Infections
  - Food
  - Household chemicals
  - Radiation
  - Occupational exposures
  - Environmental exposures

FURTHER ROLES OF MOTHERSAFE

- Emphasis on counselling and follow-up/research
- Collaborate with other Teratology Services throughout the world
- Provide education to HCPs/students through training and dissemination of evidence based factsheets
- Public Health Service



MotherSafe NSW Medications in Pregnancy & Breastfeeding Service — The Royal Hospital for Women

NAUSEA AND VOMITING OF PREGNANCY

Information in this leaflet is general in nature and should not take the place of advice from your health care provider. With every pregnancy there is a 3 to 5% risk of having a baby with a birth defect.

What is Nausea and Vomiting of Pregnancy?

Nausea and vomiting of pregnancy (NVP) affects over half of all pregnant women and can have a significant impact on the lifestyle of the pregnant woman[1, 2, 3]. Although NVP is commonly known as 'morning sickness', it can happen at any time of the day or night. Symptoms usually occur from week 6 to week 14, though may continue through the entire pregnancy. Symptoms are variable and include intermittent nausea, aversion to odours and particular foods, dry retching, vomiting and in severe cases, persistent vomiting, dehydration and electrolyte disturbances [4]. Other conditions can also cause nausea and vomiting in pregnancy and should be excluded by your doctor. The term *hyperemesis gravidarum* is used when symptoms are severe enough to require hospital admission and rehydration. *Hyperemesis gravidarum* is very rare and occurs in about one in 1000 pregnancies.

What causes Nausea and Vomiting of Pregnancy?

The cause of NVP is unclear. The nausea may be a result of the changing hormones in a woman's body to support the pregnancy [1], low blood sugar, low levels of vitamin B6 (pyridoxine) or an imbalance in potassium and magnesium. A well balanced diet should provide adequate amounts of all these vitamins and minerals. There is no way of predicting if NVP will happen in a pregnancy however many women who have had NVP during their first pregnancy will also have it in subsequent pregnancies.

Is it Nausea and Vomiting of Pregnancy harmful to the pregnancy?

Moderate levels of nausea and vomiting will not harm a developing baby[5]. Ensure you drink plenty of fluids and avoid dehydration. Try and eat a variety of foods so that you continue to get your daily requirements of vitamins, minerals and nutrients.

Settling Nausea and Vomiting of Pregnancy (Morning Sickness)[1].

The following are some suggestions which may assist in settling morning sickness

- Try to avoid any triggers, like certain smells, that make you feel sick
- Drink plenty of fluids. It's best to drink small amounts often, but not at the same time as you are eating.
- Cold or frozen drinks and foods are often better tolerated.
- Don't overeat. Eat small meals rather than a lot of food all at once.
- Avoid an empty stomach- have frequent small snacks like dry toast, crackers or fruit.
- Avoid fatty, spicy, fried and battered foods.
- Try to eat at times when you feel least sick.
- Get out of bed slowly and take your time in the morning rather than rushing.
- Eat before you get out of bed in the morning (keep crackers and water beside the bed).
- Rest when you can - fatigue can make nausea worse.
- Do not brush your teeth right after eating as this can cause nausea.
- Some herbal teas may be helpful- try peppermint tea or ginger tea.

For more information call MotherSafe: NSW Medications in Pregnancy and Breastfeeding Service on 9382 6539 (Sydney Metropolitan Area) or 1800 647 848 (Non-Metropolitan Area) Monday -Friday 9am-5pm (excluding public holidays)

MOTHERSAFE CLINIC

- Medicare covered consult with Dr Debra Kennedy and other clinicians.
- A dated referral from doctor required.
- Face-to-face at RHW Randwick or via telehealth.
- Possible reasons for referral;
  - Complex cases
  - Known exposure to teratogens
  - Considering termination due to exposure concerns

MEDICINE USE IN PREGNANCY

- Approximately 90% of pregnant women will take **at least one** medication during the course of their pregnancy.

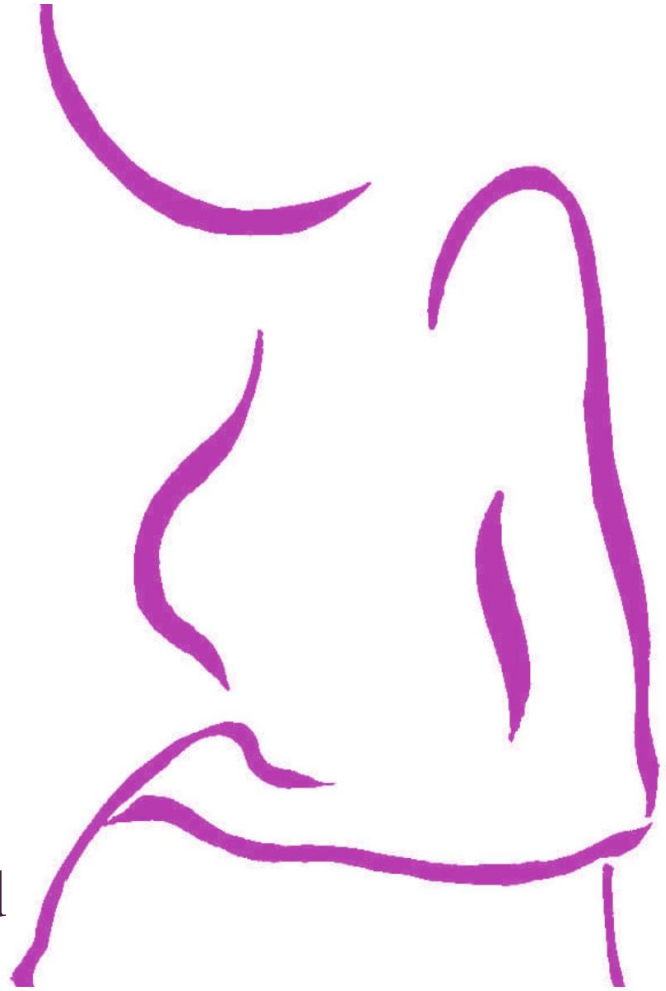
- Commonly this involves medications to manage;
  - **short-term pregnancy-induced** ailments
    - (e.g. nausea, reflux, haemorrhoids etc)
  - common **non-pregnancy-related** conditions
    - (e.g. cold and flu, hayfever, headache, musculo-skeletal pain/injuries etc)
- Many pregnant women have **pre-existing (chronic) conditions**
  - such as asthma, hypertension, depression and diabetes etc that often require them to continue to take the medications they were on prior to pregnancy
  - if left untreated, many of these conditions can cause adverse effects on the foetus and/or neonate, in addition to the possible negative impacts on maternal health

BACKGROUND CONTEXT FOR ALL PREGNANCIES

- Every pregnancy carries a **background risk of 2-3% of the baby being born with a major birth defect** (and the risk is as high as 5% if later neurodevelopmental disorders are included).
- There is also a background risk of miscarriage; **at least 15% of diagnosed pregnancies will end in miscarriage**.

➡ It is important that any risks associated with medicine exposures are expressed in relation to these background risks.

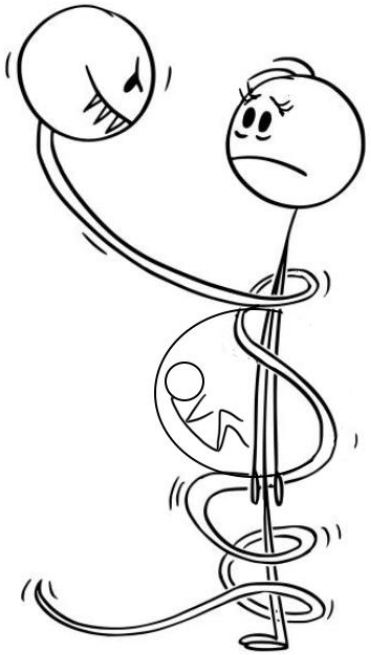
- Approximately 50% of pregnancies in Australia are unplanned so inadvertent exposures during early pregnancy often occur.



RISK PERCEPTION

A teratogen *(Greek, teraton = monster)* is any agent that causes a congenital abnormality following foetal exposure during pregnancy.
** The overall effect depends on dosage and time of exposure **

- Medicines account for less than 1% of birth defects.
- Although **most medications are not associated with a teratogenic risk**, consumers (as well as many healthcare professionals) often have concerns about the potential harmful impact on the unborn child.
- Consumers are increasingly seeking their own information on the internet and are potentially well-informed (or misinformed) as the case may be.



It is therefore important that doctors possess the ability to **confidently** and **appropriately** provide **relevant evidence-based information** and recommendations regarding medication use in pregnancy, as well as to **alleviate the concerns** of medication users who are pregnant or planning a pregnancy.

** Be mindful of what you say. Some things can not be unheard. **

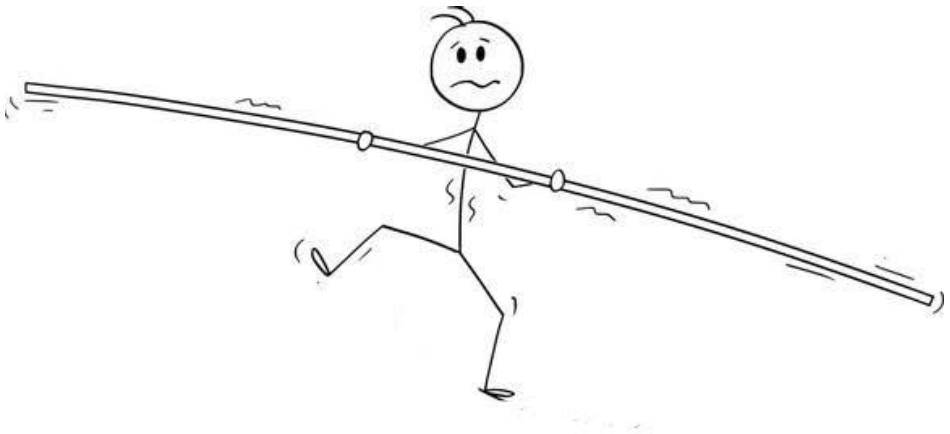
IMPORTANT CONSIDERATIONS FOR DOCTORS

Recommending/prescribing medications to pregnant women requires cautious consideration.

- Many medicines will cross the placenta so it is **important to consider the potential consequences of foetal exposure** and whether the medication is associated with increased risks of miscarriage, congenital malformations, other adverse pregnancy outcomes and/or pharmacological effects on neonate at delivery.
- BUT it is **equally important to consider the potential harmful implications of the maternal condition not being treated**.

RISK VS BENEFIT

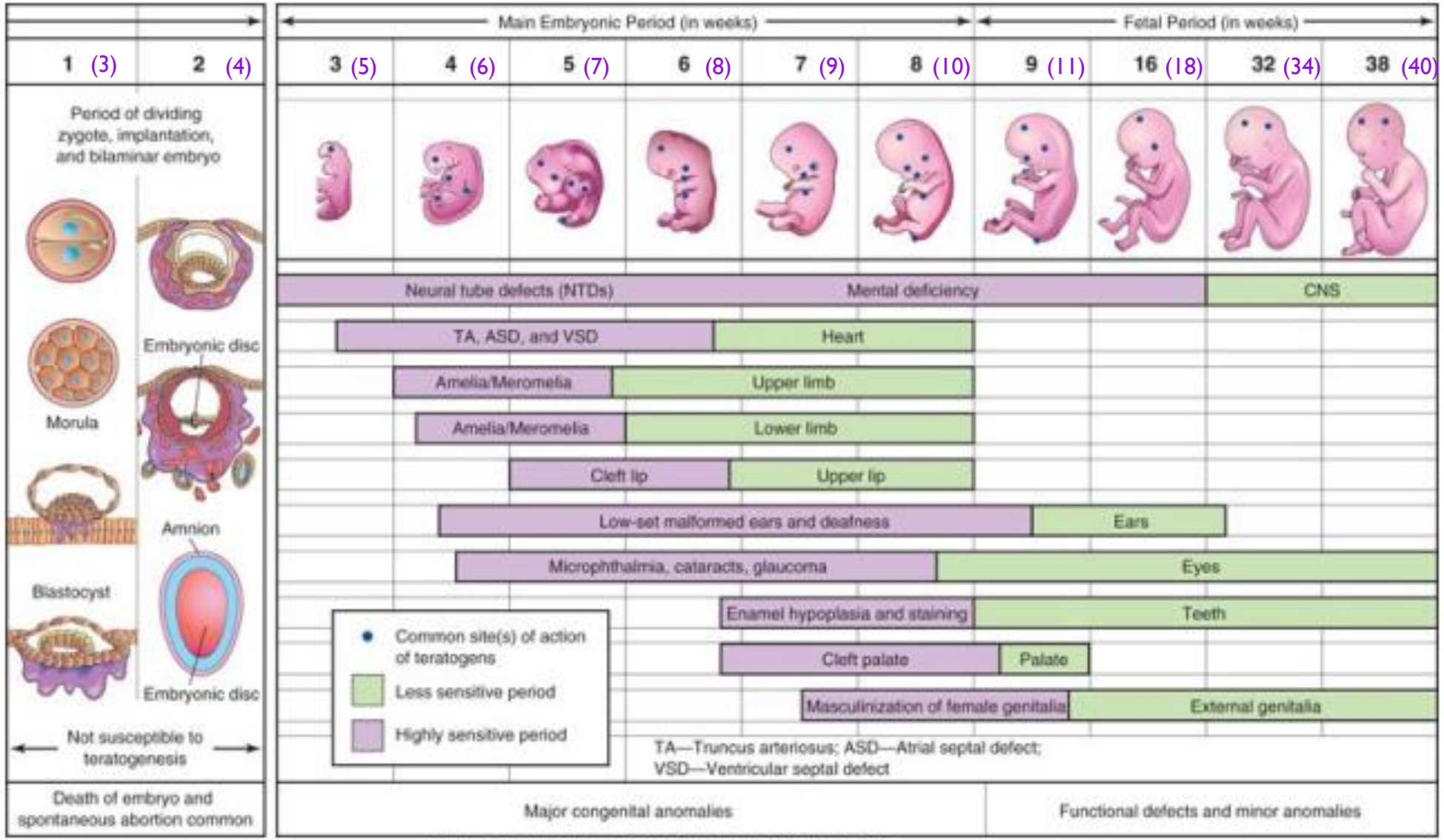
The safe use of medicines in pregnancy requires a comprehensive understanding of **risk vs benefit** profiles for individual treatments.



Dose and critical periods of development/timing of exposure must be considered when assessing risk.

CRITICAL PERIODS OF HUMAN DEVELOPMENT

LMO (1) (Last Menstrual period) (2)



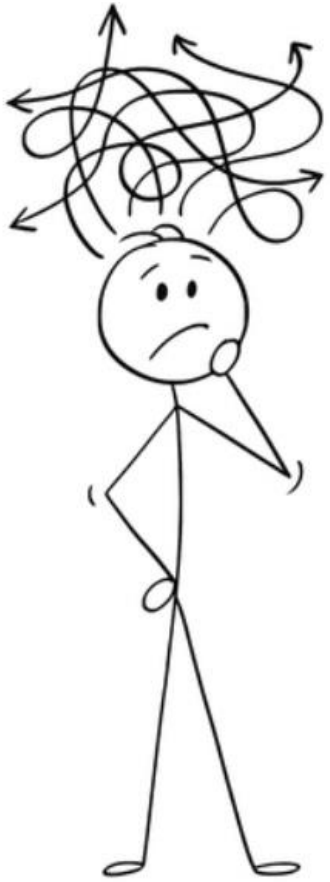
QUICK NOTE ON COMPLEMENTARY AND ALTERNATE MEDICINE USE IN PREGNANCY

- Lack of regulation across the complementary industry
- Lack of standardisation of products
- Lack of studies demonstrating efficacy
- Lack of safety studies in pregnancy

Therefore, **most complementary products won't pass a 'harm vs benefit' risk assessment regarding their use in pregnancy** because the paucity of evidence-based information means that not only is the potential "harm" is hard to determine, but the "benefit" is as well.

NB: Some complementary medicines are associated with harm in pregnancy such as andrographis (thought to have abortifacient effects), passion flower (reported to have uterine stimulant effects) and blue cohosh (potential teratogenicity, uterine stimulant and possible toxicity in infant).

CHALLENGES FOR DOCTORS



- Doctors are often very busy and may have limited time available to counsel pregnant patients and conduct in-depth research.
- Many doctors lack confidence when providing pregnancy related advice and tend to assign high levels of risk to drugs where they determine the data to be uncertain.
- Advice about medicine safety during pregnancy can vary greatly between references which creates confusion and concern.

WHEN TO REFER TO MOTHERSAFE...

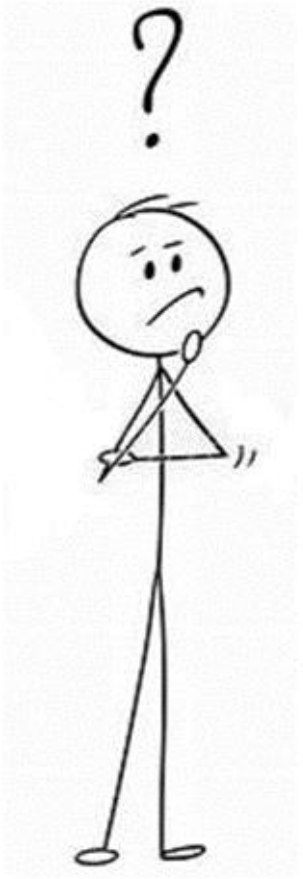
- If there is no pregnancy data or where the information available is unclear/conflicting.
- When an exposure has already occurred and the medical information suggests some risk.
- Complicated cases.
- Patient/physician anxiety.
- Whenever you do not feel confident.

If in doubt about the safety of a drug in pregnancy/breastfeeding, **always check first BEFORE advising the patient about risk**.

EXAMPLE: DIFFERENT ADVICE FROM VARIOUS REFERENCES FOR ACICLOVIR

TGA	Monthly Index of Medical Specialties (MIMS)	Australian Medicines Handbook (AMH)	RWH Pregnancy and Breastfeeding Medicine Guide
Category B3	Extracts from "Zovirax" drug monographs; **Tablets:** There have been no adequate and well controlled studies concerning the safety of acyclovir in pregnant women. It **should not be used** during pregnancy unless the benefits to the patient clearly outweigh the potential risks to the foetus. **Cold sore cream:** Aciclovir has been taken only by a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans. A post-marketing acyclovir 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 to the general population, and the appearance of birth defects showed no uniqueness or consistent pattern to suggest a common cause. Zovirax cold sore cream **should not be used** during pregnancy unless the benefits to the patient clearly outweigh the potential risk to the foetus.	**Safe to use** (extensive clinical experience).	First trimester exposure to Aciclovir has not been associated with an increased risk of congenital malformations. Adverse effects in the newborn have not been reported following in utero exposure to Aciclovir. Aciclovir is considered **safe to use** for all stages of pregnancy.

MANUFACTURER PRODUCED INFORMATION



Product information (PI) and Consumer Medicines Information (CMI) leaflets:

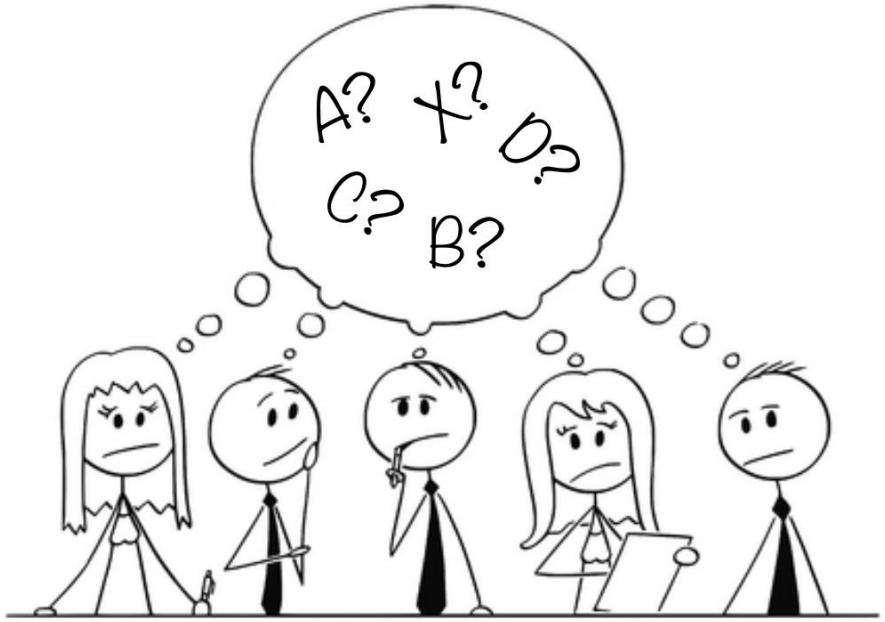
- **medico-legal documents**
- conservative/defensive wording (produced by drug company and their lawyers)
- almost universally do not recommend use in pregnancy (and breastfeeding)
- rarely are updated in line with new pregnancy/breastfeeding safety data/information
- not reliable sources for assessing safety of medicine use in pregnancy

TGA Australian Categorisation System for registered medicines in pregnancy

CATEGORY	DEFINITION
A	Drugs which have been taken by a **large number of pregnant women** and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.
B (1-3)	Drugs which have been taken by only a **limited number of pregnant women** and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. B1: Studies in animals have not shown evidence of an increased occurrence of fetal damage. B2: Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage. B3: Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
C	Drugs which, owing to their pharmacological effects**, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations**. These effects may be reversible. Accompanying texts should be consulted for further details.
D	Drugs which have caused, are suspected to have caused or may be expected to cause, **an increased incidence of human fetal malformations or irreversible damage**. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
X	Drugs which have such a high risk of causing permanent damage to the foetus that they **should not be used in pregnancy or when there is a possibility of pregnancy.**

PREGNANCY CATEGORY CONFUSION

It is very common for people, including many healthcare professionals, to not understand what the Australian pregnancy categories *actually* mean.



The system is overly simplistic which can (and often does) lead to false assumptions about medications based on their category alone.

COMMON MISCONCEPTIONS/LIMITATIONS OF THE PREGNANCY CATEGORY SYSTEM…

1. THE ALPHABETICAL LETTER CODE **IS NOT** A SIMPLE GRADUATED RANKING OF RISK.

As stated on the TGA website (but often overlooked/ignored),

the Australian pregnancy system is not hierarchical!

For example, category B drugs are *not generally* safer choices than category C drugs because the defining quality of the B grading is the lack of human pregnancy safety data associated with these drugs.

A MOVE AWAY FROM PREGNANCY CATEGORIES...

- Since 2015, the US Food and Drugs Administration's (FDA) has introduced a "Pregnancy and Lactation Labelling Rule" system which provides more comprehensive information summaries than their previous pregnancy letter categories.

- Since 2016, the Australian Medicines Handbook (AMH) has not included the Australian pregnancy categories in their drug monographs, but instead moved to narrative descriptions (citing similar reasons to the FDA).

- Since 2018, the New Zealand Formulary (NZF) has chosen to use comprehensive information from *Drugs in Pregnancy and Lactation*, in place of the Australian TGA pregnancy categories.

EXAMPLE: COMPARISON OF TWO ANTI-DEPRESSANTS

CITALOPRAM

- Category C
- Significant number of studies published internationally on SSRI use during pregnancy over the past decades.
- Maternal use of citalopram has not been associated with any increased risk of congenital malformations above baseline risk in the general population.
- Neonatal adaptive symptoms (transient and generally mild) possible at birth following use late in 3rd trimester.
- Long term behavioural and cognitive outcomes of children exposed to SSRI in utero, have shown no significant difference compared to non-exposed children.

VORTIOXETINE

- Category B3
- Published reports describing the use of Vortioxetine during pregnancy have not been located.
- As with other antidepressants, neonatal adaptive symptoms could be possible at birth, especially following use in late 3rd trimester.
- Long term studies not available.

NB: If Vortioxetine was the medicine of choice for a patient to maintain their mental health, the lack of human data would not preclude its use, but a consultation with a perinatal psychiatrist/MotherSafe would be recommended.

2. THE ASSIGNED CATEGORY DOES NOT ALWAYS REFLECT THE CURRENT SAFETY INFORMATION

- Pregnancy categories often do not change despite the availability of new (often reassuring) information.
- Once a category has been assigned to a drug, there is no defined timeframe when it must be reviewed by the TGA – instead the manufacturer is responsible for initiating a review.

* This is regularly an issue for Category B drugs. As new drugs, many are assigned a category before market release, typically based only on animal reproductive studies (not human data due to ethical constraints). It is common for the original category to remain unchanged despite increased human data over time.

EXAMPLE: MEBENDAZOLE

- Category B3
- Came into use ~ 50 years ago (1970s)
- Poorly absorbed from gut so systemic absorption is minimal
- On the WHO's list of Essential Medicines
- Untreated helminth infection increases the risk for internal bleeding leading to iron loss and anaemia, intestinal obstruction and inflammation, diarrhoea, and impaired nutrient intake, digestion, and absorption.

- More than 10,000 pregnancy exposures to mebendazole, with 1022 1st trimester and all other exposures starting in the 2nd trimester, have been reported. No adverse outcomes have been observed.

Thus, where indicated, mebendazole is considered compatible for the treatment of helminth infections occurring during pregnancy.

3. IMPACT OF MEDICO-LEGAL SPONSOR COMPANY ON DRUG CATEGORIES

Although the TGA website says that the categories have been "developed by medical and scientific experts based on available evidence", **sponsors (aka manufacturers) are allowed to legally apply "a more restrictive category than can be justified on the basis of the available data".**

Further to this, even when a drug has been assigned a "safe" category, manufacturers are permitted to make independent recommendations about use during pregnancy in their product information leaflet.

EXAMPLE: DOXYLAMINE

Sedating antihistamine

- Category A
- 1st line for NVP in the Australian Therapeutic Guidelines
- Marketed internationally for NVP

BUT

Up until very recently, manufacturer product information stated "not recommended for use in pregnancy"

After acknowledging the warning against use in pregnancy was inconsistent with the Category A classification, the TGA changed the RASML (required advisory statement for medicine labels) in January 2022 with the revised *RASML No. 6*, which removes this warning from doxylamine labelling.

NB: There is an 18 month transition period for compliance with *RASML No. 6* which will end on 1 July 2023. Consequently, many brands of doxylamine still have the old warning advising against use in pregnancy.

Some examples of different pregnancy advice depending on brand of doxylamine;

Compliant with RASML No 6 changes;

Restavite® (MIMs revision date 01 Feb 2022):

Use in pregnancy. (Category A)
Medical or pharmacist advice is required before use in pregnancy. Nonpharmacological interventions for insomnia should be considered as first-line therapy.

Not yet compliant with RASML No 6 changes;

APOHealth Sleep Assist ® (MIMs revision date 01 April 2021):

Use in pregnancy. (Category A)
Do not use during pregnancy.

Dozile ® (MIMs revision date 01 Jan 2009):

Use in pregnancy (Category A)
Dozile capsules 25 mg should be avoided during pregnancy.

4. DRUGS WITHIN THE SAME CATEGORY OFTEN DO NOT CARRY THE SAME RISK

- Categories do not differentiate between **drugs associated with significant risk compared to drugs that are associated with less risk.**
- It also does not provide information about **relative risk of the same medication at different dosages.**
- It is rare for categories to address the **impact of different dose forms** on a medicine's risk profile.

Topical or inhaled medicines are often associated with less risk than oral or parenteral medicine because there is less systemic absorption and lower maternal serum concentrations which means that transplacental passage and associated risk to the embryo is usually minimal.

EXAMPLE: COMPARISON OF RISK BETWEEN DRUGS IN SAME CATEGORY

VALPROATE

- Category D
- Associated with a significantly increased risk of birth defects and neurodevelopmental sequelae.
- Foetal valproate syndrome includes neutral tube defects, cleft palate, cardiac anomalies and minor facial dysmorphism as well as increased risk of neuro-developmental problems. Risks greater with polytherapy and with doses >1000mg/day.

PAROXETINE

- Category D
- Associated with a slightly increased risk (in some but not all studies) of heart defects.
- As the heart is formed by 10 weeks, associated increased risk would NOT be relevant for exposures after the first trimester.

EXAMPLE: COMPARISON OF DIFFERENT RISK FOR THE SAME DRUG AT DIFFERENT DOSES
FLUCONAZOLE

High Dose

- Category D
- Fluconazole is considered teratogenic at continuous daily doses (400mg/day or more) as *in utero* exposure has resulted in a pattern of congenital malformations similar to Antley-Bixler syndrome.

Low Dose

- Category D
- A single dose of fluconazole 150mg has not been associated with an increased risk of defects.

EXAMPLE: COMPARISON OF RISK FOR DIFFERENT DOSE FORMS OF THE SAME DRUG

TERBINAFINE

CATEGORY B1

Cream

"Topical preparations of terbinafine are considered safe to use in all stages of pregnancy as systemic absorption is expected to be minimal."

CATEGORY B1

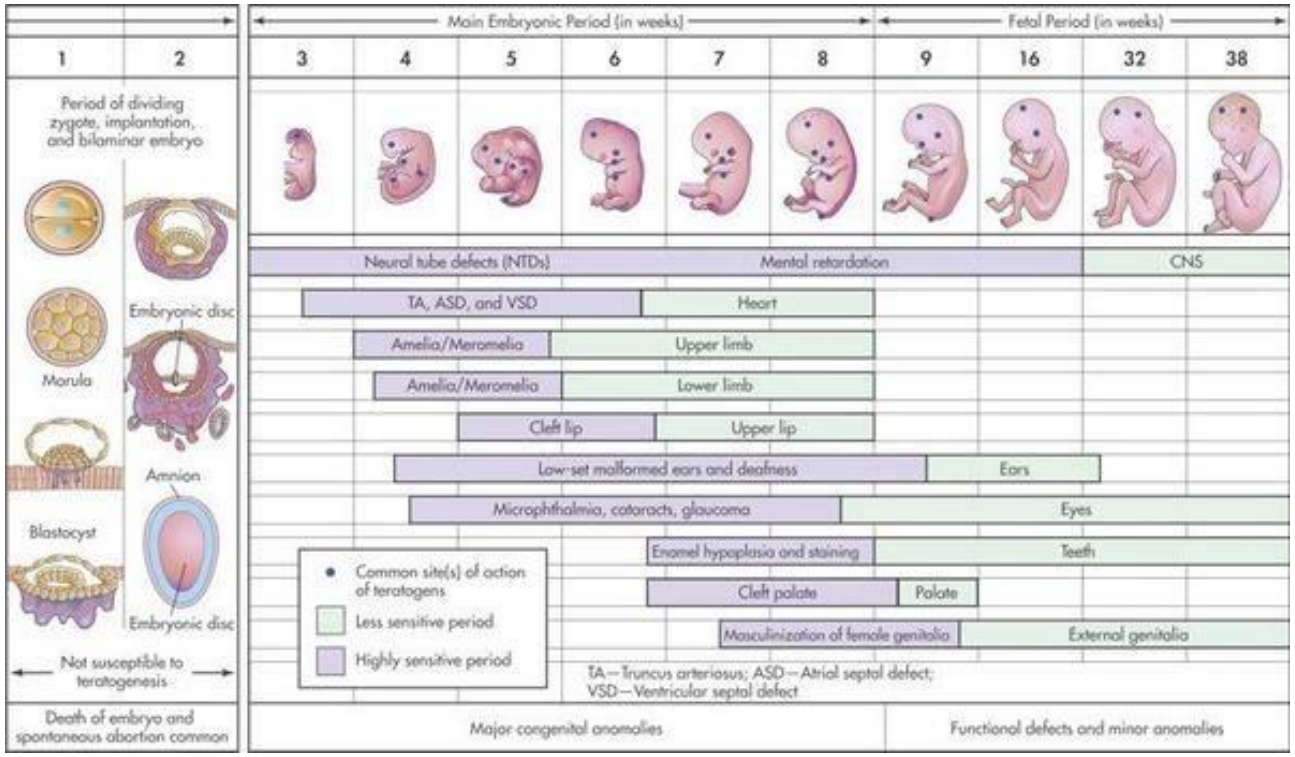
Tablet

"From the limited information available, maternal use of oral terbinafine has not been associated with an increased risk of congenital malformations however, consultation with an Infectious Diseases specialist or Clinical Microbiologist for further advice is recommended when considering oral terbinafine during pregnancy."

Extracts from the Royal Hospital for Women's Pregnancy and Breastfeeding Medicine Guide Terbinafine medication profile.

5. CATEGORIES DO NOT CONSIDER THE STAGE OF PREGNANCY

The assigned category of risk for a drug **may not be relevant for all stages of pregnancy**.



Timing of an exposure is a critical factor when determining risk.

An agent can only cause a problem if the exposure occurs during the critical period of embryonic or foetal development.

EXAMPLE: DIFFERENT RISK AT DIFFERENT GESTATIONAL TIMES
TETRACYCLINES

Category D

Considered safe if used during the first 18 weeks of pregnancy (16 weeks post-conception)

BUT

After this period, they are contra-indicated as tetracyclines can;

- inhibit bone growth in the foetus (reversible after stopping treatment; permanent bone defects do not appear to occur)
- discolour deciduous teeth

6. CATEGORIES DO NOT PROVIDE A CLINICAL CONTEXT TO RISK

- Pregnancy categories do not differentiate between use of a medicine for a more or less significant condition.
  - E.g. Doxycycline for malaria prophylaxis vs doxycycline for acne.

- They also do not consider the implications of the medical condition remaining untreated.

EXAMPLE: NICOTINE REPLACEMENT THERAPY

- Category D
- Nicotine is a toxic, highly additive compound to which any exposure during pregnancy could carry a risk to embryo and/foetus.

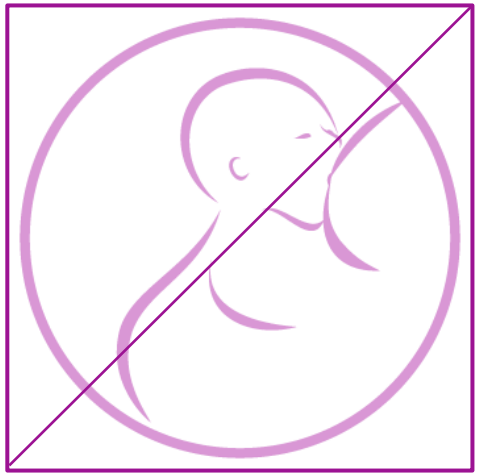
- BUT there is **strong evidence of the known risks associated with smoking during pregnancy** (increased risk of miscarriage, intrauterine growth restriction, premature delivery etc, plus health risks of second-hand smoke to the infant after birth, as well the obvious maternal health risks).

- Cigarette smoke contains >3000 different compounds, in addition to nicotine such as carbon monoxide, ammonia, hydrogen cyanide etc.

- **NRT is a harm minimisation strategy for women who have failed to quit smoking with non-pharmacological strategies.**

- Use the lowest effective dose that controls symptoms of withdrawal and cravings. Faster acting NRT (gum, lozenges or inhaler) are preferred as the total dose of nicotine is likely to be less compared to NRT patches but **all products are preferrable to smoking.**

7. AUSTRALIAN *PREGNANCY* CATEGORIES ONLY APPLY TO PREGNANCY!



They are not a reference for assessing medicine safety in breastfeeding.

NB: Some drugs that are considered safe in pregnancy, may pose risk to a breastfeeding infant (e.g. codeine). And vice versa (e.g. warfarin).

BREASTFEEDING

Breastmilk is the ideal nutrition source for infants with many benefits for both mother and baby including (but not limited to);

- Promoting mother-child bonding
- Transfer of immunoglobulins, nutrients, enzymes, growth factors, etc.
- Enhanced infant cognitive development and immunity etc.
- Reduced maternal risk of breast/ovarian cancer, type 2 diabetes and cardiovascular disease.
- Free!

NB: Not all women are able or want to breastfeed (which is more than acceptable) but for those that do, they should be supported appropriately.

COMMON REASONS FOR DRUG USE WHILE BREASTFEEDING

- Seek relief from conditions associated with the breastfeeding process
  - antibiotics for mastitis; galactogogues; antifungals for nipple thrush etc.
- Treat chronic conditions
  - epilepsy, hypertension, depression/anxiety etc.
- Treat acute conditions
  - injury; postnatal depression; infections etc.
- Alleviate symptoms of minor illness
  - common cold/hay fever; hemorrhoids etc.
- To prevent illness
  - vaccinations etc.
- Recreational
  - alcohol; caffeine, illicit substances etc.

MEDICINE USE WHILE BREASTFEEDING

MOST medicines (both OTC and prescription) are considered compatible with breastfeeding.

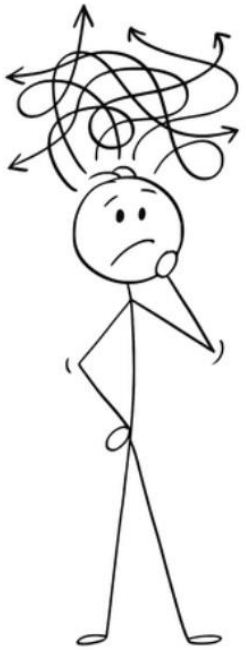
Nonetheless, women are frequently advised to stop breastfeeding (often unnecessarily) while taking a medicine.

It can be very difficult to withhold/cease breastfeeding (especially abruptly) and it is not an action without potential adverse health consequences for both mother and baby.

- baby may not transition to bottles/infant formula easily
- not all women are able to express milk, despite use of breast pumps
- can be a traumatic experience for both mother and baby
- deprives baby of the benefits from breastmilk
- may increase the risk of mastitis
- interruptions to breastfeeding may affect breastmilk supply
- may result in the mother choosing not the take the medication at all

BARRIERS TO DRUG USE IN LACTATION

- Manufacture leaflets are medico-legally defensive and almost always advise against using drugs while breastfeeding
- Lack of confidence/concerns with use of products during breastfeeding against manufacturer advice
- Paucity of published data regarding drug use in lactation
- Misinformation common from multiple sources (HCPs, online etc.)
- Breastfeeding often not valued (or at the very least, interruptions to breastfeeding are commonly viewed as being easy to do and without consequence)
- Maternal anxiety about infant safety often trumps self-care



- Maternity/infant distress
- Non-compliance with medications and/or maternal condition not treated
- Cessation of breastfeeding, either temporary or permanently

EXAMPLE: MISREPRESENTATION OF METRONIDAZOLE

Extracts from Flagyl® Product information:

Use in lactation. Metronidazole is secreted in breast milk (see Section 5.2 Pharmacokinetic Properties). In view of its tumorigenic and mutagenic potential (see Section 5.3 Preclinical Safety Data), breastfeeding is not recommended.

BUT WAIT!

Isn't Metronidazole given therapeutically to children from birth without any mention of tumorigenic or mutagenic risk???

Extract from AMH Children's Dosing Companion:

Dosage – Metronidazole

Length of course depends on the infection and its response to treatment.

Anaerobic bacterial infections

Birth (at term) – 1 month

Doses used locally may differ from those below.

Oral, 7.5 mg/kg every 12 hours.

IV, initially 15 mg/kg, then 7.5 mg/kg every 12 hours.

1 month – 18 years

Oral, 7.5 mg/kg (maximum 400 mg) 3 times a day or 10 mg/kg (maximum 400 mg) twice daily. Usual adult dose 200–400 mg every 8–12 hours.

IV, 7.5 mg/kg (maximum 500 mg) 3 times a day or 12.5 mg/kg (maximum 500 mg) twice daily (3 times a day for clostridial or CNS infections). Usual adult dose 500 mg every 8–12 hours.

Extract from Australian Medicine Handbook:

Metronidazole

Precautions | Adverse effects | Dosage | Administration advice | Counselling | Practice points

Breastfeeding

Safe to use. May cause some bitterness in milk. Use in divided doses after breastfeeding rather than single daily doses.

Drug Profile from RWH Pregnancy and Breastfeeding Medicine Guide:

Metronidazole

Search Medicine Guide

Anti-infectives

PREGNANCY | BREASTFEEDING | MISCELLANEOUS | REFERENCES | PATIENT INFORMATION

Excreted into milk	Yes
Milk to plasma ratio	0.9 (14) to 1.15 (15)
Relative infant dose	12.6 (15) to 13.5% (14)
Recommendation	Considered safe to use

Breastfeeding Summary

Metronidazole is excreted into breast milk, but adverse effects have not been reported in breastfed infants (14).

Metronidazole is considered safe to use during breastfeeding at doses of up to 400mg three times a day and observe the breastfed infant for potential adverse effects such as diarrhoea, vomiting, skin rash or thrush (3). The unpleasant taste of metronidazole (16) may be present in the breast milk.

If a single high dose treatment (2g) is required, consider withholding breastfeeding for 12 to 24 hours following administration, then resume breastfeeding (17-19).

Last Updated: 4 August 2020

WHY IS MANUFACTURER BREASTFEEDING ADVICE SO DIFFERENT TO OTHER REFERENCES?

Exclusion of breastfeeding women from drug trials (often due to ethical concerns for both mother and infant) has contributed to the **lack of lactation specific information/extensive clinical studies.**

Drug authorities (like the TGA) have **not approved** many medications for use in breastfeeding patients.

Evidence to support the use of a medicine during bresatfeeding **often only becomes available AFTER a drug is first approved for marketing**, and even then, often consists of a limited number of case studies rather than clinical drug safety studies.

Manufacturer product information regarding **medicine use in breastfeeding is rarely updated** in line with new information.

- Product information produced by manufacturers are **medico-legal documents** written from a conservative and defensive position.
- A **risk avoidance approach** of discouraging (or specifically advising against) the use of products in breastfeeding women is very common and means that the use of MANY drugs in this specific patient population falls outside the approved TGA product labelling.

EXAMPLES OF COMMON BREASTFEEDING STATEMENTS USED IN PRODUCT INFORMATION

REASSURING	May be used Unlikely to be harmful Compatible
CAUTIONARY	Only use if clearly needed Should not be used unless benefit justifies the risk Caution should be exercised
SUGGESTING AVOIDANCE	Do not take Not recommended Alternative feeding arrangements should be considered
NO SPECIFIC RECOMMENDATION	Safety has not been established Limited experience No human data

EXAMPLE: ANTIBIOTICS FOR LACTATIONAL MASTITIS

Therapeutic Guideline recommendations;

1st line agents:

1. dicloxacillin 500 mg orally, 6-hourly. If symptoms and signs resolve rapidly, 5 days of therapy may be sufficient; otherwise continue treatment for 10 days

   OR

1. flucloxacillin 500 mg orally, 6-hourly. If symptoms and signs resolve rapidly, 5 days of therapy may be sufficient; otherwise continue treatment for 10 days.

Extract from Distaph® (Dicloxacillin) product information;

Use in lactation. Dicloxacillin is distributed into milk. Therefore, caution should be exercised when dicloxacillin is administered to a nursing woman.

Extract from Staphlex® (Flucloxacillin) product information;

Use in lactation. Flucloxacillin sodium monohydrate is excreted in breast milk in trace amounts. In nursing mothers, an alternative feeding method is recommended because of the risk of allergic sensitisation in the infant.

Therapeutic Guideline recommendations for treatment of lactational mastitis continued;

For patients with **delayed nonsevere** hypersensitivity to penicillins, cefalexin can be used in most cases [Note 1]. Use:

> cefalexin 500 mg orally, 6-hourly. If symptoms and signs resolve rapidly, 5 days of therapy may be sufficient; otherwise continue treatment for 10 days.

For patients with **immediate (nonsevere or severe)** or **delayed severe** hypersensitivity to penicillins, use:

> clindamycin 450 mg orally, 8-hourly. If symptoms and signs resolve rapidly, 5 days of therapy may be sufficient; otherwise continue treatment for 10 days.

Extract from Cephalex® (Cephalexin) product information;

Use in lactation. Cephalexin is excreted in the milk. Caution should be exercised when cephalexin is administered to a nursing woman. Alternative feeding arrangements for the infant should be considered.

Extract from Dalacin® (Clindamycin) product information;

Use in lactation. Clindamycin has been reported to appear in human breast milk in ranges of 0.7 to 3.8 microgram/mL. Clindamycin has the potential to cause adverse effects on the breastfed infant's gastrointestinal flora such as diarrhoea or blood in the stool, or rash. Therefore, clindamycin is not recommended for nursing mothers.
If clindamycin is required by a nursing mother, it is not a reason to discontinue breastfeeding, but an alternate drug may be preferred. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for clindamycin and any potential adverse effects on the breastfed child from clindamycin or from the underlying maternal condition.

FOR THE RECORD:

As the excerpts from the Australian Medicine Handbook below demonstrate, ALL of these antibiotics indicated for lactational mastitis are safe to use in breastfeeding.

Dicloxacillin

Mode of action | Indications | Precautions | Adverse effects | Dosage | Administration advice

Breastfeeding

Safe to breastfeed (may cause loose bowel actions in the child).

Flucloxacillin

Mode of action | Indications | Precautions | Adverse effects | Dosage | Administration advice

Breastfeeding

Safe to breastfeed (may cause loose bowel actions in the child).

Cefalexin

Mode of action | Indications | Precautions | Adverse effects | Dosage | Administration advice

Breastfeeding

Safe to breastfeed (may cause loose bowel actions in the child). Although there are no data for ceftaroline, ceftolozane or ceftazidime with avibactam, there is no reason to suppose that they would be unsafe.

Clindamycin

Mode of action | Indications | Precautions | Adverse effects | Dosage | Administration advice

Breastfeeding

Safe to use; may cause loose bowel actions in the baby.

* Remember that paediatric suspensions of cephalexin and flucloxacillin are available and marketed for therapeutic use in young children.

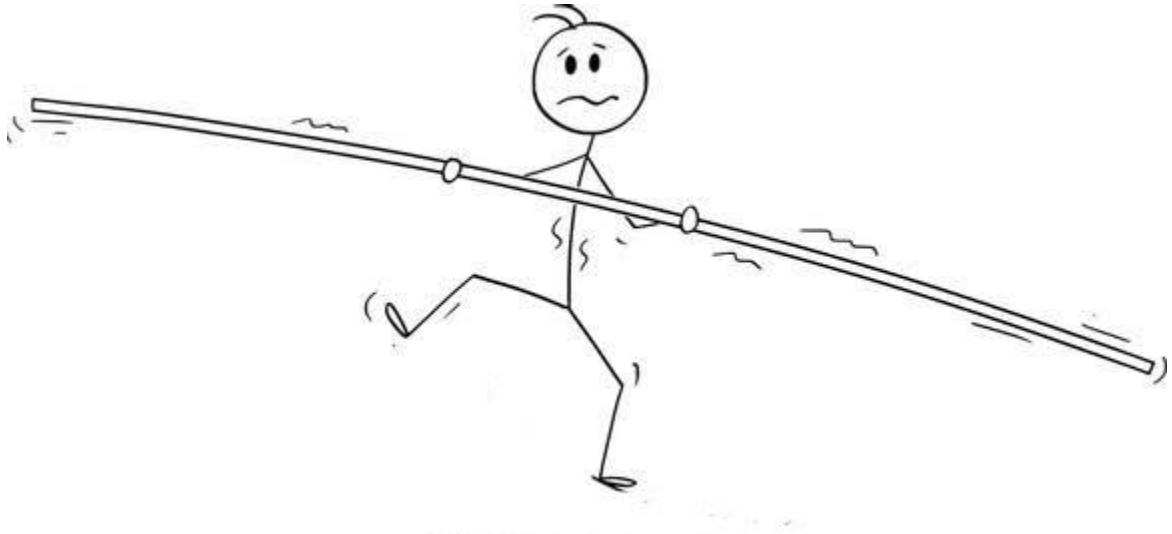
WHAT IS OFF-LABEL USE?

OFF-LABEL = use for an accepted indication that is not an approved indication (i.e. contrary to the product licence/approved TGA labelling).

- Many scenarios constitute off-label prescribing, including where the product information specifically warns against use of medications for specific patient populations (such as breastfeeding women).
- Off-label medicine use is legal and very common/often unavoidable in obstetrics/maternal and paediatric clinical practice.
- Critical use of evidence is required to support all decisions regarding "off-label" medicine use. It is all about using good quality references!
- Patients must be educated about the reasons for off-label medicine use and feel confident to provide informed consent.

RISK VS BENEFIT

The safe use of medicines in breastfeeding requires a comprehensive understanding of **risk vs benefit** profiles for both the mother and breastfeeding infant.



IMPORTANT CONSIDERATIONS WHEN RATIONALISING DRUG USE IN LACTATION

(POTENTIAL FOR HARM)

I. Transfer of a drug into breastmilk
- Influenced by the pharmacokinetics of drug, dose, drug form, maternal pharmacogenetics etc.

II. Clinical relevance to the infant of drug presence in breastmilk
- Age of baby, bioavailability of drug, duration of use, anticipated infant side effects etc.

III. Drug influence on breastmilk quantity and quality

IV. Are there safer alternatives available or strategies to minimize exposure?

(BENEFIT)

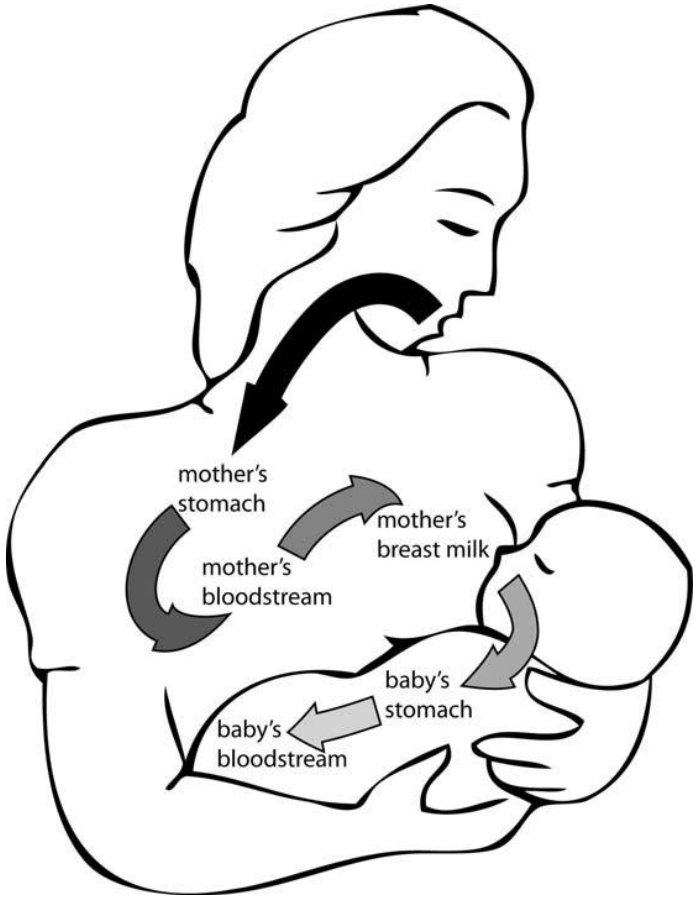
- Importance of treating the maternal condition
- Importance of supporting continued breastfeeding

I. DOES THE DRUG **TRANSFER** INTO BREASTMILK?

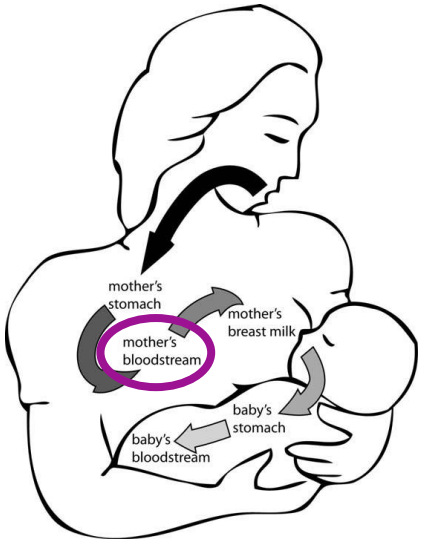
Most drugs will pass into breastmilk (usually in very small amounts).

- Primarily transfer occurs via passive diffusion, a two-way process where drugs move **into and out** of breastmilk as the mother's blood levels change.

- The extent of transfer is dependent on several factors.



FACTORS INFLUENCING **EXCRETION** INTO BREASTMILK



1. MATERNAL PLASMA CONCENTRATION

- Most important determinant of drug penetration into milk.
- Almost without exception, as the level of medication in the mother's bloodstream rises, the concentration in milk increases as well.

Medicines with low maternal plasma concentration are not expected to be transferred into breastmilk in clinically relevant quantities.

- Drugs not absorbed from GIT (e.g. nystatin, simethicone)
- Drugs with poor bioavailability (e.g. mebendazole, loperamide)
- Topical products with minimal systemic absorption (creams, inhaled corticosteroids/beta-2 agonists, intranasal sprays and eye/ear drops)

FACTORS INFLUENCING **EXCRETION** INTO BREASTMILK

2. HALF LIFE

Drugs with short half lives are preferred in breastfeeding as they are quickly eliminated from the maternal plasma, reducing infant exposure.

- Feeds can often be timed to avoid expected peak plasma/milk concentrations (e.g. sumatriptan, topical glyceryl trinitrate).

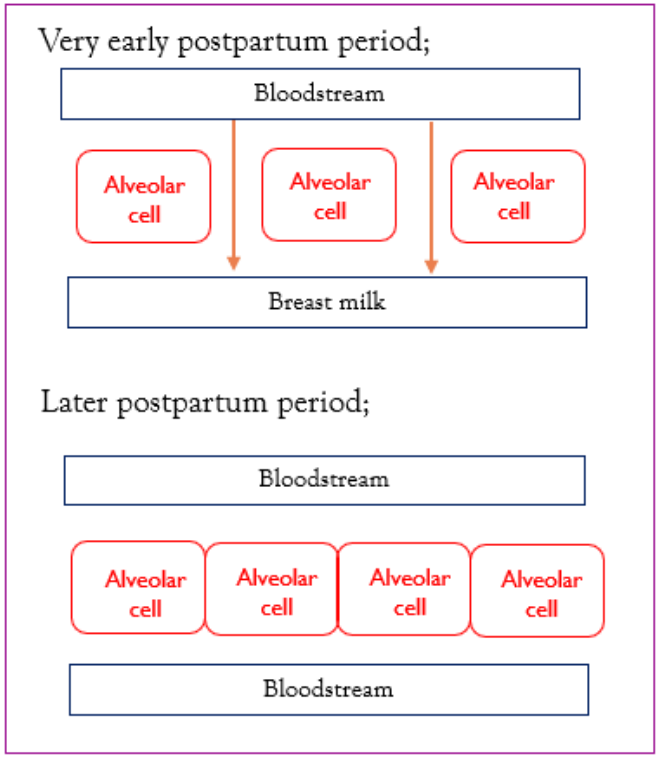
Caution is advised with drugs (or their active metabolites) that have long paediatric half-lives as they can accumulate in the infant's plasma over time.

- e.g. barbiturates, benzodiazepines, naproxen etc.

FACTORS INFLUENCING **EXCRETION** INTO BREASTMILK

3. MOLECULAR WEIGHT

Large molecules / high molecular weight drugs (> 800 daltons) are too big to cross the cellular membrane barrier and pass into breastmilk (e.g. enoxaparin, new monoclonal antibodies).



Exception: In the very early post-partum period, wide intercellular gaps in the mother's milk ducts facilitate the passage of immunoglobulins into breastmilk. This also briefly allows increased passage of medicines (particularly larger sized drugs) than would occur later.

4. PROTEIN BINDING

Drugs that are highly protein bound (> 90-95%) are less likely to cross in breastmilk because it is the unbound faction of drug that transfers into milk (e.g. warfarin, sodium valproate).

FACTORS INFLUENCING **EXCRETION** INTO BREASTMILK

5. ACID/BACE BALANCE

Drugs with a pKa > 7.2 (weakly basic) may transfer more readily into breast milk.

Drugs cross membranes in an un-ionised form. Breastmilk is slightly more acidic than blood so it attracts weakly basic drugs (e.g. oxycodone). These drugs can become ionised in the milk, making them less able to diffuse back into the blood, potentially becoming 'trapped' in the breastmilk.

6. LIPOPHILICITY

Medicines with high lipid solubility may transfer more into breastmilk by dissolution into the fat component of milk.

NB: Milk composition varies according to infant age and phase of feed.

KEY FACTORS INFLUENCING **EXCRETION** INTO BREASTMILK

7. MATERNAL PHARMACOGENOMICS

- The influence of pharmacogenomics, or the interaction between drugs and a person's genetic makeup, is a growing area of understanding.
- Genetic testing for genes that can influence drug metabolism is not standard practice, but may become more available in the future.

EXAMPLE: Codeine

- Codeine is variably metabolised to morphine by the cytochrome P450 (CYP) 2D6 enzyme.
- Ultrarapid metaboliser phenotype occurs in up to 10% of Caucasians, 1-2% of Asians, 21% of people from the Middle East and 29% of Ethiopians.
- Repeated codeine doses in ultra-rapid metabolisers can produce significant amounts of morphine in breastmilk which could lead to lethal levels in newborn.
- Case of neonatal CNS depression and death.
- Codeine is consequently relatively contra-indicated in breastfeeding.

II. CLINICAL RELEVANCE OF A DRUG IN BREASTMILK

1. AGE OF BABY

One of the most important factors when determining risk via breastmilk.

- Premature vs full term
- Neonates may have decreased drug metabolism and excretion due to immature liver enzymes.
- Age also affects;
  - sucking behavior and duration spent at each breast
  - the quantity of milk consumed per feed
  - the interval between feeds
  - total infant dose (mg/kg)

Newborn

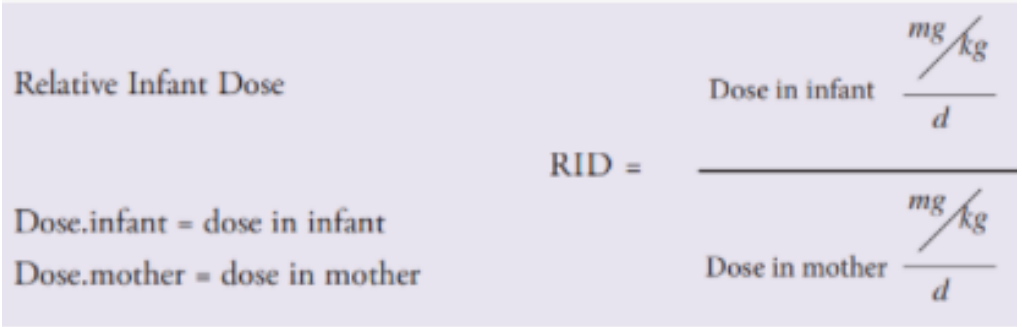
Toddler

RISK TO INFANT VIA THE BREASTMILK DECREASES WITH INCREASING AGE

CLINICAL RELEVANCE OF A DRUG IN BREASTMILK

2. RELATIVE INFANT DOSE

- Few medicines that enter breastmilk reach levels of significance, especially following short-term use.
- One of the most popular methods of estimating risk to infant is the RID.

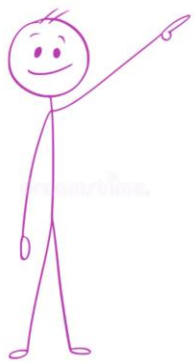


Generally, **drugs with a relative infant exposure of <10% of the weight-adjusted maternal dose are considered compatible** with breastfeeding (although there are some exceptions).

Quetiapine

Psychotropics

Excreted into milk	Yes
Milk to plasma ratio	0.41 (13)
Relative infant dose	0.02% (15)
Recommendation	Considered safe to use



Breastfeeding Summary

There is limited safety information available following the use of quetiapine during breastfeeding.

Very small amounts of quetiapine are excreted into breast milk (13, 15-17), but use with caution in women breastfeeding pre-term infants. Observe the infant closely for potential adverse effects such as excessive drowsiness, poor feeding and unusual sleeping pattern changes. Inform neonatal care providers immediately if any adverse effects are noted in the breastfed infant.

Last Updated: 13 April 2021

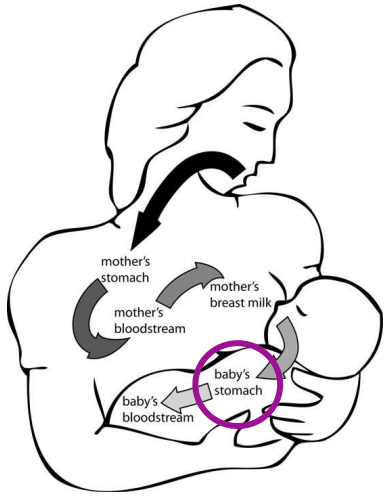
BE AWARE...

- Higher doses of a medication may pose increased exposure risk to an infant than a low dose of the same medication.
  - e.g. low dose vs high dose aspirin

- A small number of drugs are potentially dangerous to infants, even in small amounts and therefore exposure should be avoided completely.
  - Oral isotretinoin and chemotherapy agents (generally contraindicated)
  - Radioactive agents (contraindicated but expressed milk can be used after waiting the required time period for radioactive decay)

CLINICAL RELEVANCE OF A DRUG IN BREASTMILK

3. ABSORPTION FROM INFANT'S GUT



After ingestion, a drug delivered via the breastmilk must traverse the infant's gastrointestinal tract prior to absorption.

- Acid labile medications are safe in breastfeeding because any drug present in breastmilk is destroyed by the infant's gut before absorption.
- The absorption of some drugs can be decreased when ingested with calcium/milk (doxycycline).

Oral bioavailability of a drug can be a useful tool to estimate drug absorption by the infant.

- Some medications are administered intravenously because they are very poorly absorbed orally (e.g. aminoglycosides). Therefore, although maternal serum concentrations and excretion into the breastmilk may be high, the oral absorption by the infant will be low.

CLINICAL RELEVANCE OF A DRUG IN BREASTMILK

4. POTENTIAL FOR INFANT SIDE EFFECTS

- **Infant age is the most significant factor to determine risk potential via the breastmilk.**
- Comparing the RID against the therapeutic paediatric dose (if one exists) can help to gauge the likelihood of infant effects and what they might be.

- Some drugs may require the infant to be monitored for potential effects.
  - CNS-active drugs such as opiates have the potential to sedate infants (particularly neonates) which can lead to serious adverse outcomes like respiratory depression or failure to thrive/poor feeding etc.
  - Some drugs with highly variable milk levels (e.g. lamotrigine) can make risk assessments difficult and require close monitoring of the infant.
  - Some drugs can irritate the infant gastrointestinal tract and cause diarrhoea, constipation, and occasionally syndromes such as pseudomembranous colitis.

WHAT IF A MEDICATION WAS SAFE TO TAKE DURING PREGNANCY?

In pregnancy the foetus often receives much higher levels of medicines than a breastfed infant BUT **some medications taken safety during pregnancy may not be safe during breastfeeding**.

Safety considerations are often very different during breastfeeding. For example;

- In utero, the maternal system clears all drugs from the infant's circulation, whereas postpartum, drug elimination relies solely on the newborn's clearance mechanisms.
- Some drug effects like CNS depression can be of greater consequence for an infant breathing on its own outside the womb.

NB: Some medicines used during pregnancy may need dosage adjustments before breastfeeding to prevent infant toxicity postpartum as maternal metabolism/drug clearance return to pre-pregnancy levels.

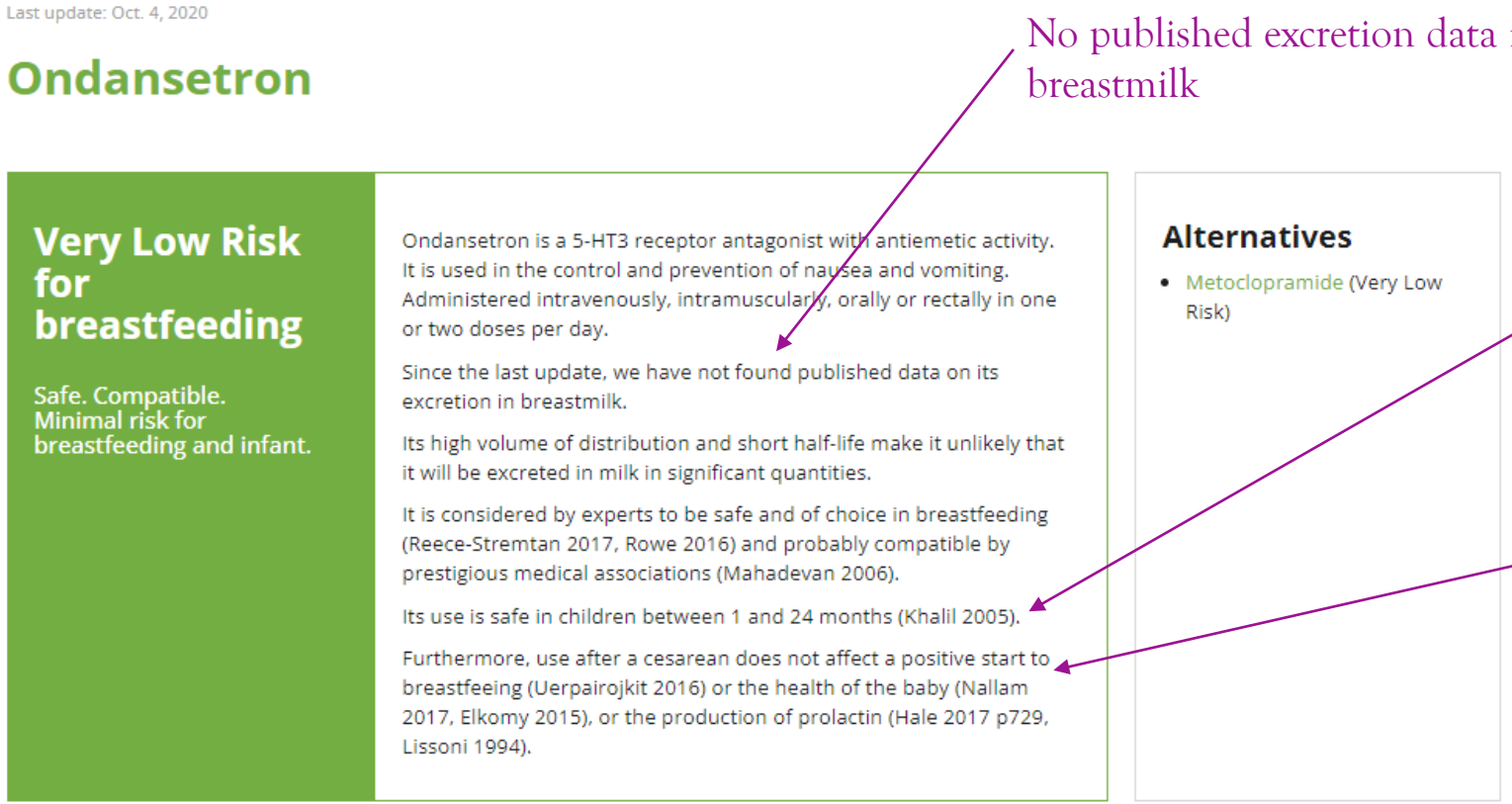
Remember that the TGA pregnancy categories *only* relate to pregnancy (not breastfeeding).

CLINICAL RELEVANCE OF A DRUG IN BREASTMILK

5. PAEDIATRIC EXPERIENCE WITH DRUG

Drugs used with safety in neonates are generally not anticipated to cause harm in breastfeeding because excretion into breastmilk will be almost always be much less than a therapeutic paediatric dose.

Example Drug Profile from e-lactancia:



Last update: Oct. 4, 2020

Ondansetron

Very Low Risk for breastfeeding

Safe. Compatible. Minimal risk for breastfeeding and infant.

Ondansetron is a 5-HT3 receptor antagonist with antiemetic activity. It is used in the control and prevention of nausea and vomiting. Administered intravenously, intramuscularly, orally or rectally in one or two doses per day.

Since the last update, we have not found published data on its excretion in breastmilk.

Its high volume of distribution and short half-life make it unlikely that it will be excreted in milk in significant quantities.

It is considered by experts to be safe and of choice in breastfeeding (Reece-Stremtan 2017, Rowe 2016) and probably compatible by prestigious medical associations (Mahadevan 2006).

Its use is safe in children between 1 and 24 months (Khalil 2005).

Furthermore, use after a cesarean does not affect a positive start to breastfeeing (Uerpairojkit 2016) or the health of the baby (Nallam 2017, Elkomy 2015), or the production of prolactin (Hale 2017 p729, Lissoni 1994).

Alternatives

- Metoclopramide (Very Low Risk)

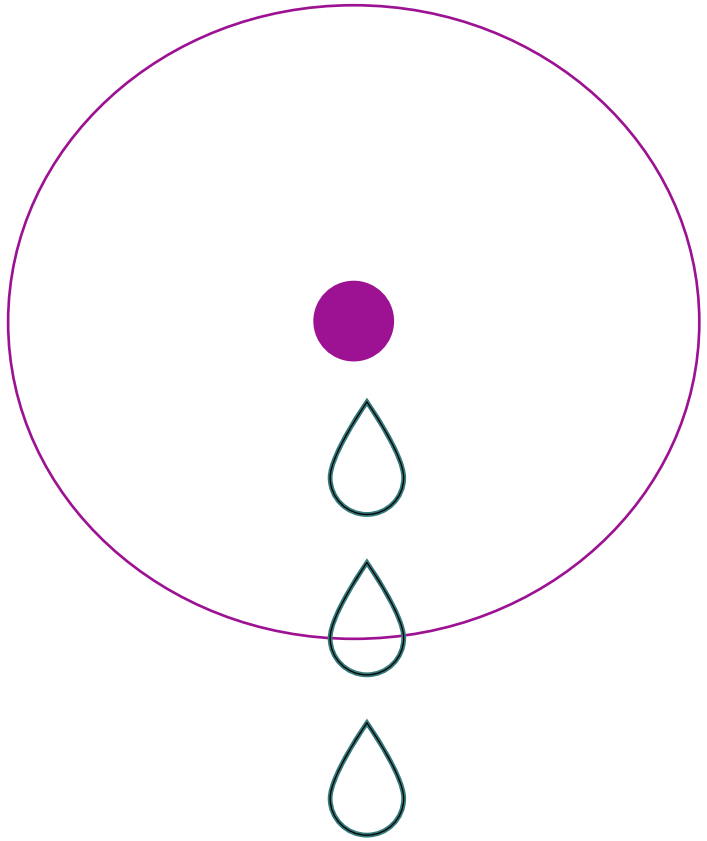
No published excretion data in breastmilk

Paediatric use from 1 month

Commonly used during early postpartum period

III. DOES THE DRUG IMPACT ON MILK SUPPLY/QUALITY?

- Some drugs can **increase** breastmilk production.
  - Metoclopramide
  - Domperidone
- Some drugs can **supress** breastmilk production.
  - Bromocriptine
  - Pseudoephedrine
  - Oestrogens



- Drugs that decrease milk production may affect infant growth and development.
- Difficulty with low breastmilk supply can lead to earlier cessation of breastfeeding.

ASSESSING BENEFIT OF EXPOSURE;

REASON FOR MEDICATION USE

Harm vs BENEFIT

- Some medications are essential for the well-being of the mother
  - Antidepressants, antibiotics etc.

- Some medications are more discretionary
  - Cosmetic botox etc.
  - Complementary medications

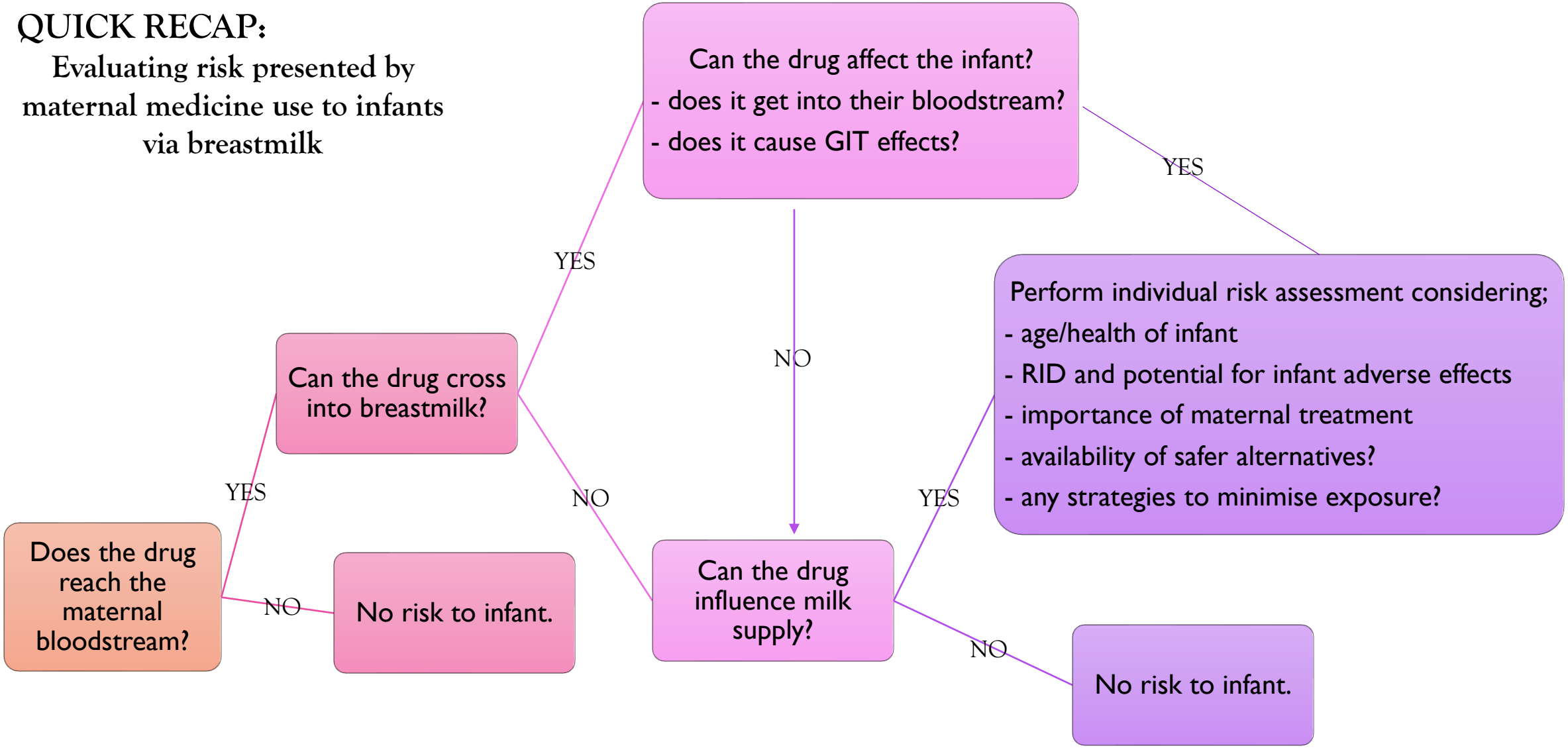
SPECIAL NOTE ON POSTPARTUM MATERNAL MENTAL HEALTH

- Encourage mothers with symptoms of depression/mental health disorders to seek treatment and continue breastfeeding where desired. **The majority antidepressant/psychotropics can be used with safety during breastfeeding.**

- Untreated or poorly treated postpartum depression/anxiety can lead to many negative outcomes for mother/infant/family such as;
  - Can lead to long-term dysfunction, either directly or indirectly via disruption of a healthy home life.
  - At its worst, can involve violent behaviour, irrational thinking and a significantly increased risk of suicide.

QUICK RECAP:

Evaluating risk presented by maternal medicine use to infants via breastmilk



PRINCIPLES FOR PRESCRIBING IN PREGNANCY

- Topical preparations should be considered before oral treatments (*if efficacious*) because less systemic absorption means less (if any) exposure to foetus.
- Always consider dose and period of gestation when making risk assessments, as well as consequences of maternal condition not being treated.
- The TGA pregnancy category system has a number of limitations and should NOT be used as a sole guide for assessing safety of medicines in pregnancy.
- Drugs that have been widely used for many years are preferable to newer alternatives as they generally have more human pregnancy data BUT the drug must be *effective* otherwise there is no point in taking it.
- Use the lowest *effective* dose for the shortest duration of time.
- Individualised approach to harm vs benefit assessment.
- Ensure discussion and education that allows the parents to give informed consent about medication choices.

GENERAL COUNSELLING PRINCIPLES:

- Consider the potential impact of word choice and phrasing of advice.
- Anticipate and address potential barriers that could undermine patient confidence in your advice
  - Negative information in the product information leaflet
  - Pregnancy category that is not in line with current data
  - Conflicting information from other HCP's
- Provide simple but evidence based information about exposures and/or treatments. It is important to deliver the information at a level that the patient will understand.
- Tailor your approach to the situation; advice given pre-exposure may differ from post-exposure.

PRINCIPLES OF DRUG USE DURING LACTATION

- STEP ONE: Evaluate the infant for risk – exercise more caution with premature infants/neonates etc.

- Avoid unnecessary medications (e.g. herbals drugs, high dose vitamins).
- Use topical products if available (*if efficacious*).
- Recommend medicines with greatest level of lactation safety data but ensure they are *efficacious* otherwise there is no point in taking them.
- Advise mothers to monitor for potential drug-related effects in infant (if relevant).
- Check for any effect on lactation.
- In the absence of breastfeeding data, consider other parameters (such as drug kinetics, paediatric experience) that might assist with determining risk.

- Individualise approach to harm vs benefit assessment.
- Ensure discussion and education that allows the parents to give informed consent about medication choices.

TAKE HOME POINTS FOR BREASTFEEDING

- Do not assume that medications that are safe in pregnancy will automatically be safe in breastfeeding (and vise versa).
- **Health of mother is critical to her ability to look after her baby.**
- Most medicines can be taken by breastfeeding mothers without interruption or risk to infant. Very few medications are contraindicated in breastfeeding, but some may require the infant to be monitored.
- Remember that the risk to infant via breastmilk decreases as age of the baby increases.

CHECK LACTMED!

Call/Refer to MotherSafe when in doubt.

SO ...WHAT OTHER REFERENCES TO USE?

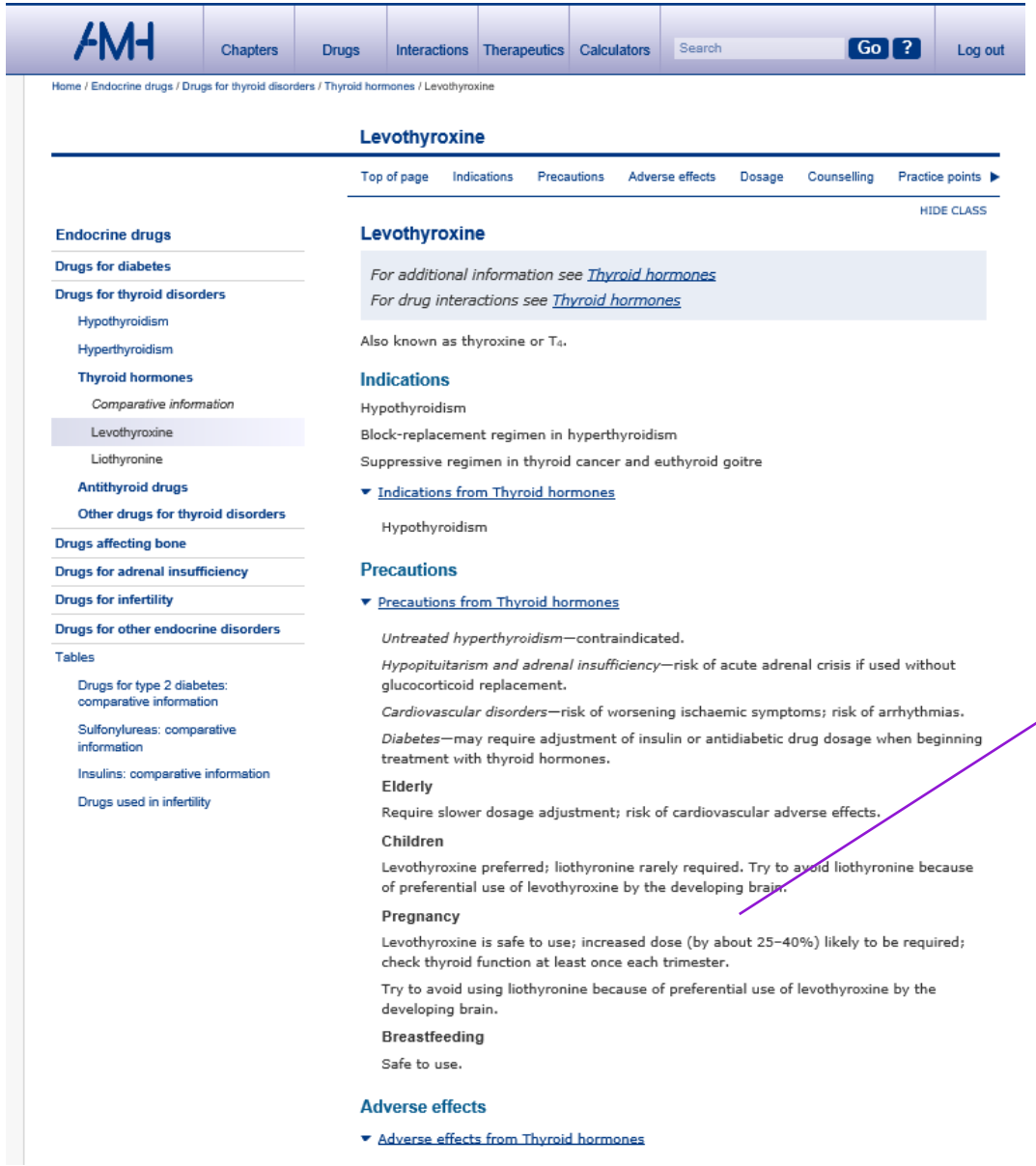
Need up-to-date and well organised information on pregnancy to enable practitioners to be in a better position to make critical decisions.

- Australian Medicine Handbook (AMH)
- The Royal Women's Hospital Pregnancy and Breastfeeding Medicine Guide (http://thewomenspbmg.org.au)
- Australian Therapeutic Guidelines
- Drugs in Pregnancy & Lactation, Briggs G
- CIAP - Micromedex/Reprotox (can access within NSW Health)

FREE!

- Australian Immunisation Handbook
- Organization of Teratology Information Specialists (now called Mothertobaby) (www.mothertobaby.org)
- MotherSafe (in NSW) or other Drug/Pregnancy Drug Information Service
- MotherSafe factsheets (www.mothersafe.org.au)
- UKTIS – BUMPS factsheets (www.medicinesinpregnacy.org)

Australian Medicines Handbook;



Pregnancy

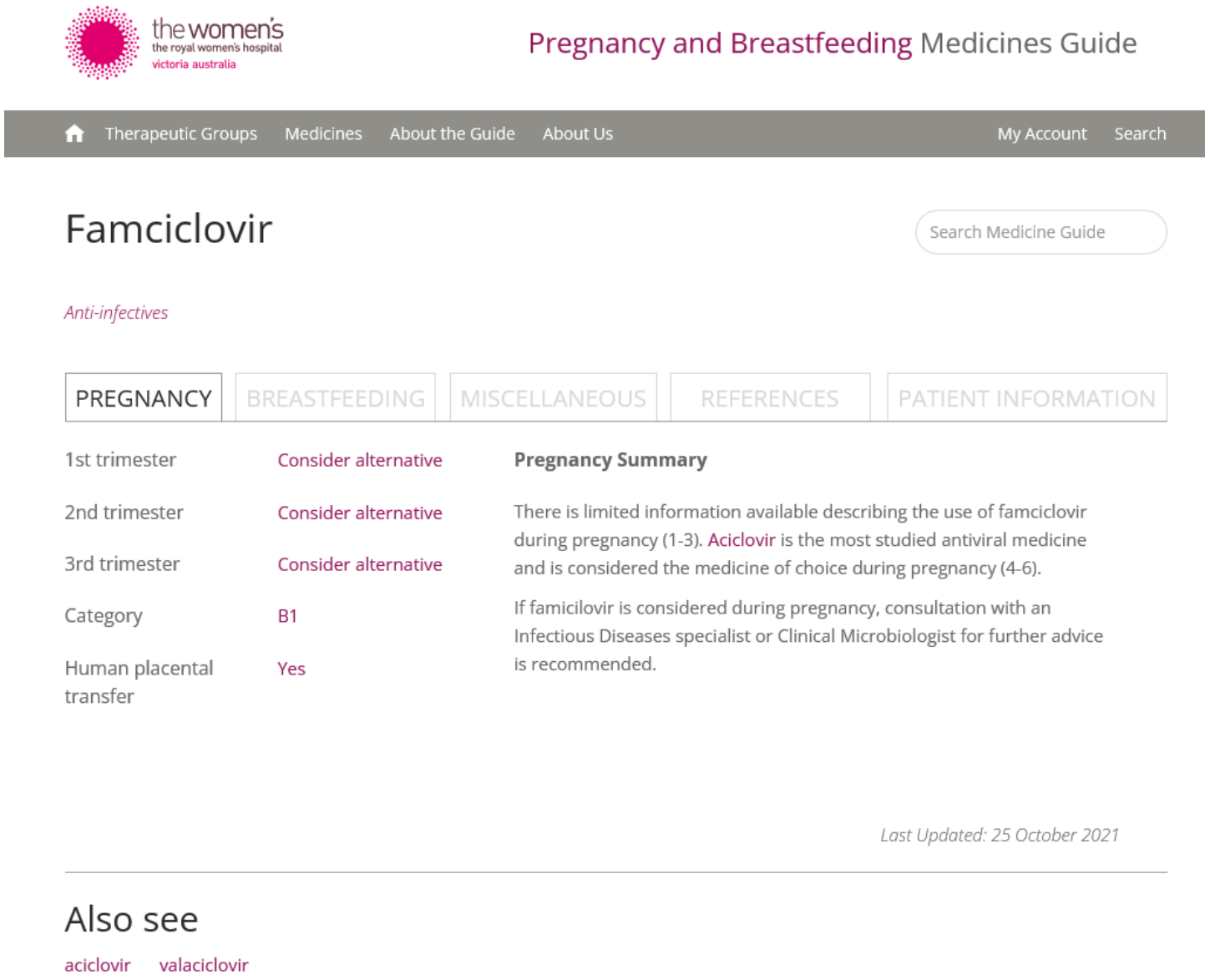
Levothyroxine is safe to use; increased dose (by about 25–40%) likely to be required; check thyroid function at least once each trimester.

Try to avoid using liothyronine because of preferential use of levothyroxine by the developing brain.

Breastfeeding

Safe to use.

The Royal Women's Hospital (Vic), Pregnancy and Breastfeeding Medicines Guide;



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Pregnancy and Breastfeeding Medicines Guide

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Famciclovir

Search Medicine Guide

Anti-infectives

PREGNANCY | BREASTFEEDING | MISCELLANEOUS | REFERENCES | PATIENT INFORMATION

1st trimester	Consider alternative
2nd trimester	Consider alternative
3rd trimester	Consider alternative
Category	B1
Human placental transfer	Yes

Pregnancy Summary

There is limited information available describing the use of famciclovir during pregnancy (1-3). Aciclovir is the most studied antiviral medicine and is considered the medicine of choice during pregnancy (4-6).

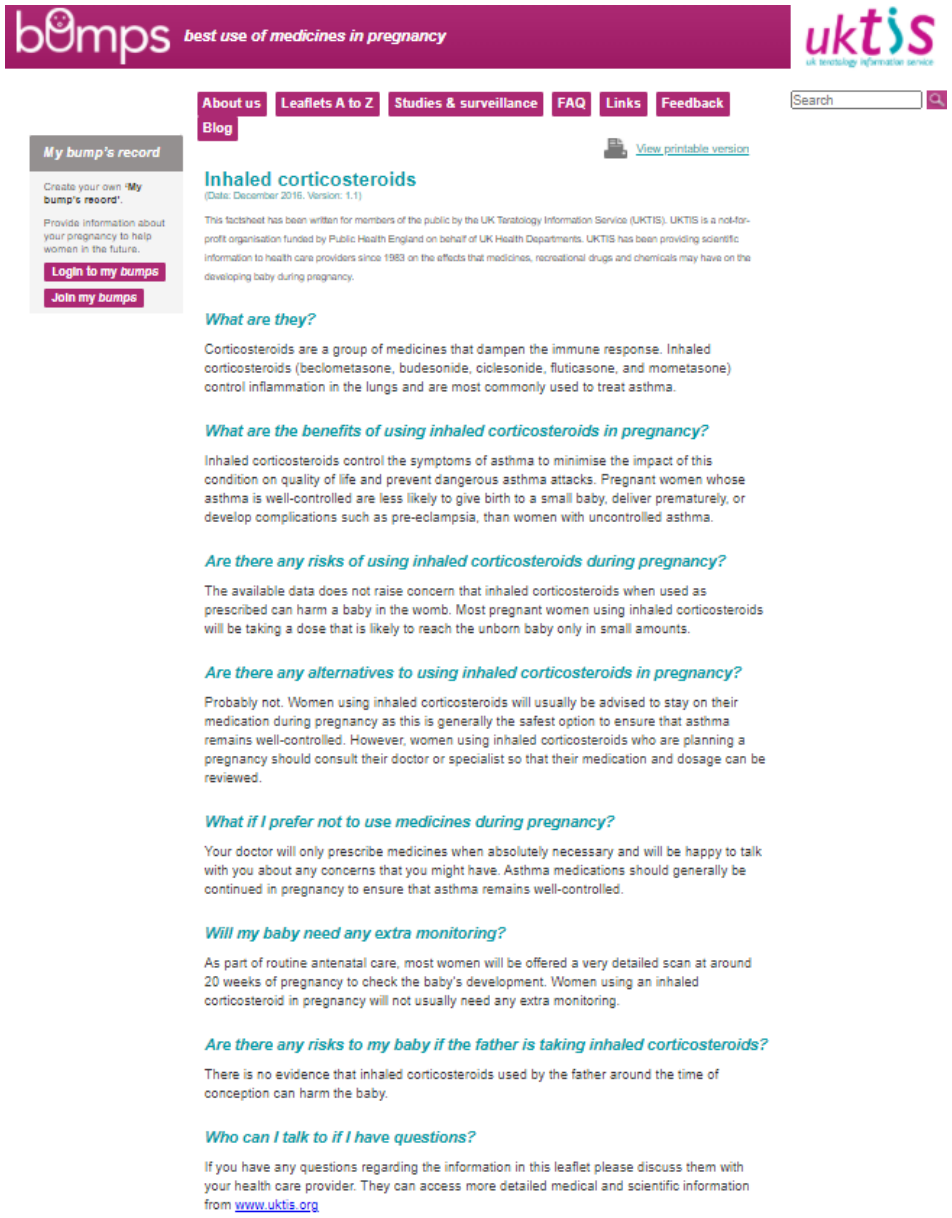
If famicilovir is considered during pregnancy, consultation with an Infectious Diseases specialist or Clinical Microbiologist for further advice is recommended.

Last Updated: 25 October 2021

Also see

aciclovir valaciclovir

Examples of free evidence based factsheets;



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Inhaled corticosteroids

(Date: December 2016. Version: 1.1)

This factsheet has been written for members of the public by the UK Teratology Information Service (UKTIS). UKTIS is a not-for-profit organisation funded by Public Health England on behalf of UK Health Departments. UKTIS has been providing scientific information to health care providers since 1983 on the effects that medicines, recreational drugs and chemicals may have on the developing baby during pregnancy.

What are they?

Corticosteroids are a group of medicines that dampen the immune response. Inhaled corticosteroids (beclometasone, budesonide, ciclesonide, fluticasone, and mometasone) control inflammation in the lungs and are most commonly used to treat asthma.

What are the benefits of using inhaled corticosteroids in pregnancy?

Inhaled corticosteroids control the symptoms of asthma to minimise the impact of this condition on quality of life and prevent dangerous asthma attacks. Pregnant women whose asthma is well-controlled are less likely to give birth to a small baby, deliver prematurely, or develop complications such as pre-eclampsia, than women with uncontrolled asthma.

Are there any risks of using inhaled corticosteroids during pregnancy?

The available data does not raise concern that inhaled corticosteroids when used as prescribed can harm a baby in the womb. Most pregnant women using inhaled corticosteroids will be taking a dose that is likely to reach the unborn baby only in small amounts.

Are there any alternatives to using inhaled corticosteroids in pregnancy?

Probably not. Women using inhaled corticosteroids will usually be advised to stay on their medication during pregnancy as this is generally the safest option to ensure that asthma remains well-controlled. However, women using inhaled corticosteroids who are planning a pregnancy should consult their doctor or specialist so that their medication and dosage can be reviewed.

What if I prefer not to use medicines during pregnancy?

Your doctor will only prescribe medicines when absolutely necessary and will be happy to talk with you about any concerns that you might have. Asthma medications should generally be continued in pregnancy to ensure that asthma remains well-controlled.

Will my baby need any extra monitoring?

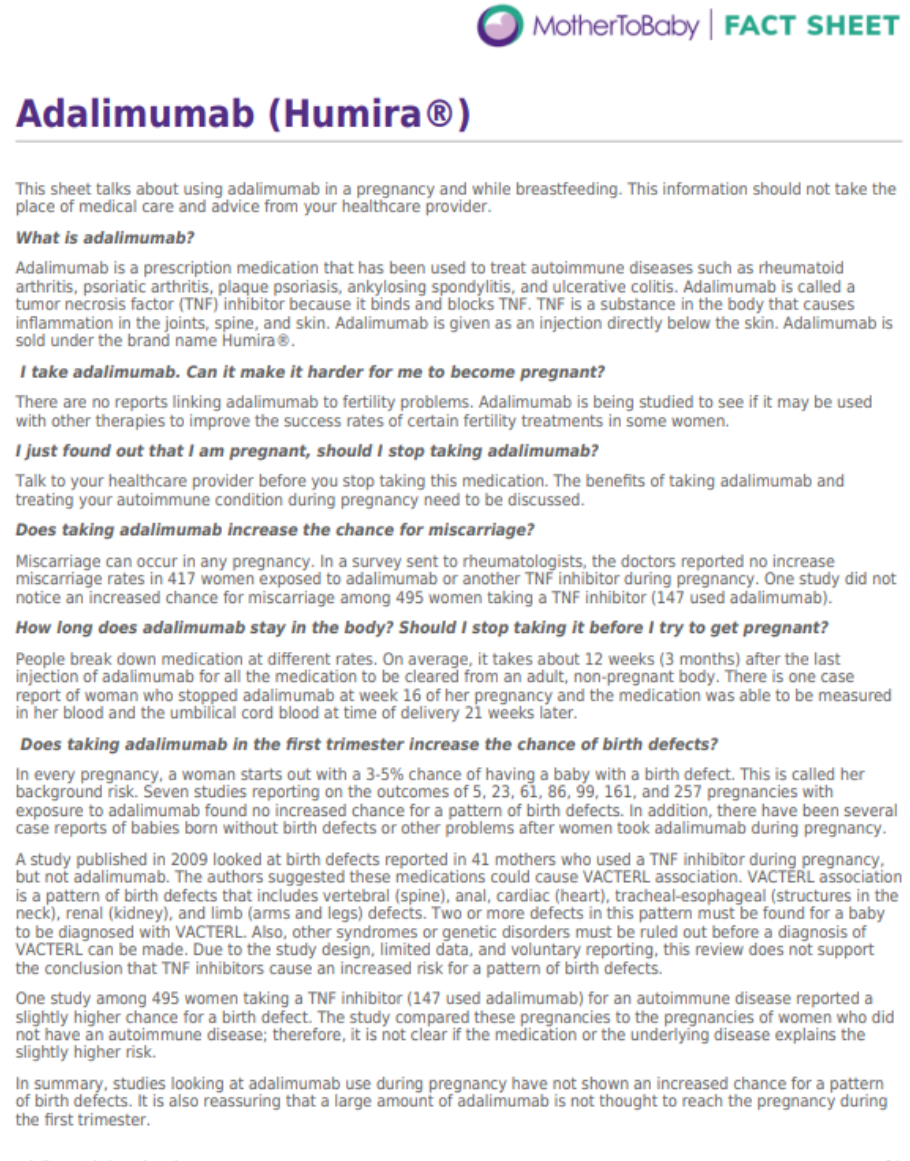
As part of routine antenatal care, most women will be offered a very detailed scan at around 20 weeks of pregnancy to check the baby's development. Women using an inhaled corticosteroid in pregnancy will not usually need any extra monitoring.

Are there any risks to my baby if the father is taking inhaled corticosteroids?

There is no evidence that inhaled corticosteroids used by the father around the time of conception can harm the baby.

Who can I talk to if I have questions?

If you have any questions regarding the information in this leaflet please discuss them with your health care provider. They can access more detailed medical and scientific information from www.uktis.org



MotherToBaby | FACT SHEET

Adalimumab (Humira®)

This sheet talks about using adalimumab in a pregnancy and while breastfeeding. This information should not take the place of medical care and advice from your healthcare provider.

What is adalimumab?

Adalimumab is a prescription medication that has been used to treat autoimmune diseases such as rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, and ulcerative colitis. Adalimumab is called a tumor necrosis factor (TNF) inhibitor because it binds and blocks TNF. TNF is a substance in the body that causes inflammation in the joints, spine, and skin. Adalimumab is given as an injection directly below the skin. Adalimumab is sold under the brand name Humira®.

I take adalimumab. Can it make it harder for me to become pregnant?

There are no reports linking adalimumab to fertility problems. Adalimumab is being studied to see if it may be used with other therapies to improve the success rates of certain fertility treatments in some women.

I just found out that I am pregnant, should I stop taking adalimumab?

Talk to your healthcare provider before you stop taking this medication. The benefits of taking adalimumab and treating your autoimmune condition during pregnancy need to be discussed.

Does taking adalimumab increase the chance for miscarriage?

Miscarriage can occur in any pregnancy. In a survey sent to rheumatologists, the doctors reported no increase miscarriage rates in 417 women exposed to adalimumab or another TNF inhibitor during pregnancy. One study did not notice an increased chance for miscarriage among 495 women taking a TNF inhibitor (147 used adalimumab).

How long does adalimumab stay in the body? Should I stop taking it before I try to get pregnant?

People break down medication at different rates. On average, it takes about 12 weeks (3 months) after the last injection of adalimumab for all the medication to be cleared from an adult, non-pregnant body. There is one case report of woman who stopped adalimumab at week 16 of her pregnancy and the medication was able to be measured in her blood and the umbilical cord blood at time of delivery 21 weeks later.

Does taking adalimumab in the first trimester increase the chance of birth defects?

In every pregnancy, a woman starts out with a 3-5% chance of having a baby with a birth defect. This is called her background risk. Seven studies reporting on the outcomes of 5, 23, 61, 86, 99, 161, and 257 pregnancies with exposure to adalimumab found no increased chance for a pattern of birth defects. In addition, there have been several case reports of babies born without birth defects or other problems after women took adalimumab during pregnancy.

A study published in 2009 looked at birth defects reported in 41 mothers who used a TNF inhibitor during pregnancy, but not adalimumab. The authors suggested these medications could cause VACTERL association. VACTERL association is a pattern of birth defects that includes vertebral (spine), anal, cardiac (heart), tracheal-esophageal (structures in the neck), renal (kidney), and limb (arms and legs) defects. Two or more defects in this pattern must be found for a baby to be diagnosed with VACTERL. Also, other syndromes or genetic disorders must be ruled out before a diagnosis of VACTERL can be made. Due to the study design, limited data, and voluntary reporting, this review does not support the conclusion that TNF inhibitors cause an increased risk for a pattern of birth defects.

One study among 495 women taking a TNF inhibitor (147 used adalimumab) for an autoimmune disease reported a slightly higher chance for a birth defect. The study compared these pregnancies to the pregnancies of women who did not have an autoimmune disease; therefore, it is not clear if the medication or the underlying disease explains the slightly higher risk.

In summary, studies looking at adalimumab use during pregnancy have not shown an increased chance for a pattern of birth defects. It is also reassuring that a large amount of adalimumab is not thought to reach the pregnancy during the first trimester.

PATERNAL EXPOSURES

Example of a MotherSafe factsheet:

Paternal medicine exposures during pregnancy are not a problem as there is no blood connection between a man and the developing baby.

Paternal radiotherapy, chemotherapy and a small number of medicines may affect male fertility.

MotherSafe NSW Medications in Pregnancy & Breastfeeding Service — The Royal HOSPITAL FOR WOMEN

Paternal exposures

Information in this leaflet is general in nature and should not take the place of advice from your health care provider. With every pregnancy there is a 3 to 5% risk of having a baby with a birth defect.

What is paternal exposure?
Paternal exposure refers to exposure of the father to medicines, radiation, chemicals or drugs of dependence in the period before pregnancy, around conception or during pregnancy.

Medication: paternal exposure before pregnancy and at time of conception
There is clear evidence that a small number of medications taken by the father may be associated with reduced fertility. Other medications may be associated with reduced sexual function which may also decrease the likelihood of the man's partner getting pregnant.[1]

In general, there is no evidence that paternal use of medication prior to or at the time of conception is associated with an increase in birth defects or other harmful outcomes in any developing pregnancy.[1]

Medication: paternal exposure during pregnancy
During pregnancy, there is no blood connection between a man and his partner's unborn baby. As a result, medications in general taken by the the father will not cause birth defects or have any other harmful effects. Semen may contain very small amounts of medication but the concentration is so low as to be considered an irrelevant exposure.[1]

Chemotherapy and radiation
The effects of chemotherapy on male fertility are dependent on the specific agent and the dose and the timing of the exposure. Many agents have a substantial impact on sperm quality and quantity which may then affect fertility. For many agents fertility can return in time. In some situations sperm banking prior to chemotherapy may be considered. Most evidence suggests that children born to fathers previously exposed to chemotherapy do not have an increased risk of birth defects or other harmful outcomes. However, most health bodies would suggest waiting 3 months after finishing chemotherapy before trying to conceive.[2]This is the time it takes to completely replace the chemotherapy exposed sperm with new, unexposed sperm.

Paternal radiation exposure through **radiotherapy** may affect fertility but often sperm counts return to normal.[1] Evidence suggests there is no increased risk of birth defects or other abnormalities in children of fathers who have previously had radiotherapy.[2]However, men may be advised by their treating doctors to wait several months after radiotherapy before their partners try to conceive. This allows time for replacement of radiation exposed sperm with unexposed sperm.

Paternal diagnostic radiology (X-Rays and scans) and paternal workplace exposure to radiation (within normal accepted limits) are not associated with significantly increased risks of birth

For more information call MotherSafe: NSW Medications in Pregnancy and Breastfeeding Service on 9382 6539 (Sydney Metropolitan Area) or 1800 647 848 (Non-Metropolitan Area) Monday –Friday 9am-5pm (excluding public holidays)

MotherSafe NSW Medications in Pregnancy & Breastfeeding Service — The Royal HOSPITAL FOR WOMEN

defects or other harmful outcomes when exposure is prior to pregnancy, around conception or during pregnancy.[3]

If a man requires **radionuclide treatment**, it is advised to wait several months after treatment before trying to conceive.[4]This too, is to allow for replacement of radiation exposed sperm with unexposed sperm.

Waiting times before conception after chemotherapy, radiotherapy and radionuclide treatment should be confirmed with the treating specialist.

Recreational drugs and alcohol
Paternal use of alcohol has been associated with reduced fertility but there is no evidence to suggest an increased risk of birth defects or other harmful effects. Paternal cigarette smoking and use of other recreational drugs such as marijuana, cocaine, methamphetamine and ecstasy may also have fertility effects but have not been implicated in increasing the risk of birth defects.[1]

Workplace exposure
A wide variety of exposures can occur in the workplace. These may involve chemicals and radiation. Although there may be potential effects on **fertility**, these can be mimimised by employers ensuring that proper occupational health and safety measures are always in place. In the case of chemicals, employers should provide good ventilation and relevant personal protective equipment (PPE) such as gloves and gowns. It is also important for individuals to use general measures such as washing hands before eating or leaving the premises.

There is no evidence of an association between a father's workplace exposure and birth defects. However, a man occupationally exposed to chemicals should consider leaving contaminated clothing in the workplace in order to prevent directly exposing his pregnant partner.[1]

References

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*** MIMS/Manufacturer Product Information are <u>not</u> reliable sources for assessing the safety of medicines in breastfeeding! ***

RECOMMENDED DRUGS IN LACTATION RESOURCES

FREE!

- Lactmed – Drug and Lactation Database from National Library of Medicine https://www.ncbi.nlm.nih.gov/books/NBK501922/
- e-lactancia www.e-lactancia.org/
- Organization of Teratology Information Specialists (now called Mothertobaby) factsheets www.mothertobaby.org
- The UK Breastfeeding network factsheets www.breastfeedingnetwork.org.uk/drugs-factsheets/
- Inside Radiology www.insideradiology.com.au
- Australian Immunisation Handbook
- MotherSafe Service and factsheets www.mothersafe.org.au
- State-based obstetric drug information services

- Australian Medicines Handbook (AMH)
- Hale's Medications and Mother's Milk www.halesmeds.com
- The Royal Women's Hospital (Vic) Pregnancy and Breastfeeding Guide https://thewomenspbmg.org.au
- Drugs in Pregnancy & Lactation, Briggs G
- Micromedex/Reprotox (access within CIAP; NSW Health)

SPECIAL MENTION: LACTMED

- FREE online well-resourced, fully-referenced and peer-reviewed database
- Regularly updated

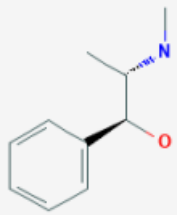
NIH U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006-. Pseudoephedrine. [Updated 2020 Apr 20].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Pseudoephedrine

Revised: April 20, 2020.

CASRN: 90-82-4



Drug Levels and Effects

Summary of Use during Lactation

Although the small amounts of pseudoephedrine in breastmilk are unlikely to harm the nursing infant, it may cause irritability occasionally. A single dose of pseudoephedrine decreases milk production acutely and repeated use seems to interfere with lactation. Mothers with newborns whose lactation is not yet well established or in mothers who are having difficulties producing sufficient milk should not receive pseudoephedrine. A treatment scheme has been reported for mothers with hypergalactia that uses pseudoephedrine to decrease milk supply.[1]

Drug Levels

Maternal Levels. A single oral dose of 60 mg of pseudoephedrine in 3 women resulted in peak milk levels of less than 1 mg/L 1 hour after the dose.[2] Other authors used data from this study to calculate the amount excreted in milk to be 5.5% of the weight-adjusted maternal dosage.[3]

After a 60 mg oral dose of immediate-release pseudoephedrine, peak milk levels averaging 698 mcg/L occurred 1.7 hours after the dose and half-life in milk was 5.5 hours. A fully breast-fed infant would receive a dose of 4.3% (range 2.2 to 6.7%) of the maternal weight-adjusted dose.[3]

Infant Levels. Relevant published information was not found as of the revision date.

Effects in Breastfed Infants

Mothers reported irritability was reported in 20% of infants exposed to pseudoephedrine in one study of breastfeeding mothers.[4]

All adverse reactions in breastfed infants reported in France between January 1985 and June 2011 were compiled by a French pharmacovigilance center. Of 174 reports, pseudoephedrine was reported to cause adverse reactions in 4 infants, primarily agitation.[5]

Effects on Lactation and Breastmilk

After a single dose of pseudoephedrine 60 mg orally in 8 nursing mothers, there was a mean 24% decrease in milk production over the following 24 hours. No change in blood flow to the breast was detected that could explain the decreased milk production; there was a 13.5% decrease in serum prolactin after pseudoephedrine, but this change did not achieve statistical significance. Oxytocin levels were not measured.[3]

Alternate Drugs to Consider

Oxymetazoline

References

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Substance Identification

Substance Name

Pseudoephedrine

CAS Registry Number

90-82-4

Drug Class

Breast Feeding