13. Safety of medication use during pregnancy and breastfeeding

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1. INTRODUCTION

- Medication use during pregnancy and breastfeeding should always rely on a favorable risk-benefit balance.
- Most drugs are prescribed to pregnant or lactating women in off-label use.
- Discontinuing abruptly a needed treatment can lead to an exacerbation of the maternal disease, which itself can pose a risk for the unborn or breastfed child.
- Most of the drugs cross the placenta.
- Most of the drugs are excreted in human milk in small amounts, which rarely leads to significant doses in the infant.
- In the general population, 2-4% of children are born with a major birth defect, of which less than 10% are considered drug related.
- Risks related to drug interference with the developmental and reproductive processes are not the same throughout pregnancy and lactation.
  - 20-70 days after the first day of the last menstruation period: risk of structural malformations.
  - During the fetal period: risk of growth restriction, some forms of structural malformations, fetal death, functional impairment, and transplacental carcinogenesis.
  - Pre and early postnatal exposure: risk of behavior, reproduction, endocrine, immune, and various other physiological functions impairment.
  - Lactation: risk of toxicity mainly linked to the infant's ability to metabolize and excrete the drug and the volume of milk ingested both of which are time-varying parameters.
- Very few drugs justify a termination of pregnancy**.**
- **In CF patients the potential benefit of treatment most often outbalances the potential risk for the unborn child.**

2. RISK ASSESSMENT IN PREGNANCY

- To assess the risk of a drug for the unborn child, a few parameters should be considered:
  - timing of exposure
  - systemic availability of the drug and/or ability of the drug to cross the placenta
  - potential spectrum of teratogenic and fetotoxic effects.
- If equally effective, well-established compounds in their class should be preferred. Drugs associated to theoretical risks, conflicting results or with limited safety data should not be considered as drugs of first choice in pregnant CF patients, unless they are associated to very limited systemic absorption.

3. RISK ASSESSMENT IN LACTATION

To assess the risk of the drug for the breastfed child, a few parameters should be considered:

- **Relative Infant Dose (RID)**:
  - It is the most clinically relevant parameter available to evaluate the level of drug exposure for the infant through breast milk.
  - RID is a weight normalized parameter calculated by dividing the dose of a drug ingestion via milk (mg/kg/day) by the mothers' dose in mg/kg/day.
- **The kind of breastfeeding**
  - Level of exposure is correlated to the volume of ingested milk (full breastfeeding > partial breastfeeding > before milk comes in).
- **The level of risk of drug accumulation for the breastfed child**, is linked to**:**
  - Drug pharmacokinetics: parent or active metabolites with long half-lives
  - The infant's ability to handle small amounts of drugs (premature < full term < 3 months old infant < 9 months old infant).
- **The level and kind of drug toxicity** depends on the pharmacological profile.

4. RECOMMENDATIONS

- **Tables 1-6** summarize published evidence and recommendations for the use of drugs during pregnancy and lactation.
  - Of note that, at the time of writing very little human data are published on the safety of CFTR modulators (ivacaftor, lumacaftor) during pregnancy and lactation.

5. ADHERENCE

- Many women will take it upon themselves to stop their treatment or will reduce the doses during pregnancy by fear for the unborn child. The same is true during breastfeeding if it's not breastfeeding itself that is interrupted → Therefore, treatment adherence should be carefully monitored and regularly discussed.

6. INFORMATION SOURCES

- The disclaimers by drug manufacturers and regulatory authorities, although understandable from the medico legal perspective, are not applicable to guide drug choice in pregnancy → Therefore, for therapeutic decisions, specialized information sources providing available evidence-based information should always be used.
- A non-exhaustive list is shown at the end of this chapter.

Table 1: Antibiotics in pregnant and lactating CF patients (Copyright© 2016 Karger Publishers, Basel, Switzerland[1])

DRUG	PREGNANCY			LACTATION		
	Safety data	**Compatibility**	**Recommendations**	**Level of exposure**	**Compatibility**	**Recommendations**
Penicillins	Numerous human data	Drug of choice in CF pregnant patient	If necessary, combination therapy with a beta-lactamase inhibitor can be used (e.g. clavulanic acid, tazobactam).	RID <2%	Drug of choice in CF lactating patient	Intravenous use often linked to poor oral bioavailability and subsequent limited systemic exposure in the suckling infant. May alter gastro-intestinal flora of the suckling infant.
Cephalosporins	Numerous human data	Drug of choice in CF pregnant patient	If equally effective, well-established compounds of the class should be preferred (e.g. cefuroxime, ceftriaxone).	RID <2%	Drug of choice in CF lactating patient	Intravenous use often linked to poor oral bioavailability and subsequent limited systemic exposure in the suckling infant. May alter gastro-intestinal flora of the suckling infant.

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Carbapenems	Limited human data	Second line treatment in CF pregnant patient	Imipenemn and meropenems should be used only in the absence of a safer alternative.	RID <2%	Second line treatment in CF lactating patient	Poor oral bioavailability and subsequent limited systemic exposure in the suckling infant. If effective, the most documented compounds of the class should be preferred (e.g. imipenem).
Monobactam	Limited human data	Second line treatment in CF pregnant patient	Aztreonam should be used only in the absence of a safer alternative.	RID <2%	Second line treatment in CF lactating patient	Poor oral bioavailability.
Macrolides	Numerous human data for azithromycin, clarithromycin, erythromycin	Drug of choice in CF pregnant patient	If equally effective, well-established compounds of the class should be preferred (e.g. azithromycin, clarithromycin, erythromycin). Other macrolides should be used only in the absence of a safer alternative.	RID <2%	Drug of choice in CF lactating patient	If effective, the most documented compounds of the class should be preferred (i.e. azithromycin, clarithromycin, erythromycin).
Quinolones	Numerous human data for norfloxacin and ciprofloxacin	Second line treatment in CF pregnant patient	Norfloxacin and ciprofloxacin can be used in the absence of a safer alternative.	RID >5%	Second line treatment in CF lactating patient	Theoretical risk of irreversible damage to joint cartilage. If effective, the most documented compounds of the class should be preferred (i.e. ciprofloxacin). Local use is safe for the breastfed infant.

Aminoglycosides	Limited human data	To be used with caution	Should be used only in life-threatening infections because of their limited risk of fetal oto- and nephro-toxicity. Therapeutic Drug Monitoring should be performed to prevent toxicity and inefficiency of the treatment. Inhaled tobramycin can be used during pregnancy.	RID <2%	Second line treatment in CF lactating patient	Poor oral bioavailability. After intravenous use, avoid breastfeeding during the two hours following the injection (maximal concentration). Inhaled tobramycin is safe for the breastfed infant.
Tetracyclines	Numerous human data for doxycycline	To be used with caution	Doxycycline can be used in the absence of a safer alternative until week 15 of pregnancy. Avoid after week 15 due to the risk of dental discoloration or growth inhibition of the long bones.	RID >5%	To be used with caution	Prolonged use (>3 weeks) is not advised because of dental discoloration. Short term use (<3 weeks) is compatible with breastfeeding. Most tetracyclines bind to calcium, thus inhibiting their absorption by the suckling infant (doxycycline binds less).
Colistin	Limited human data	To be used with caution	Intravenous use should be reserved for life-threatening infections. Inhaled colistin can be used during pregnancy.	RID unknown	Second line treatment in CF lactating patient	Inhaled colistin is safe for the breastfed infant.

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Sulfonamides	Numerous human data	Second line treatment in CF pregnant patient	During the first trimester, high dose or long term use of sulfonamides, such as sulfamethoxazole-trimethoprim combined with a folate antagonist (e.g. trimethoprim) should be associated with folic acid intake (1-5 mg/d), even though evidence is lacking to support its efficacy. Sulfonamides use until birth can be associated with a rise in bilirubin, especially in premature neonates.	RID > 5% for trimethoprim	Second line treatment in CF lactating patient	In the absence of safer alternative, the most documented compounds of the class should be preferred (i.e. cotrimoxazole).
Clindamycin	Numerous human data	Second line treatment in CF pregnant patient	Should be used only in the absence of a safer alternative.	RID<2%	Second line treatment in CF lactating patient	Should be used only in the absence of safer alternative.

Table 2: Antifungal agents in pregnant and lactating CF patients (Copyright © 2016 Karger Publishers, Basel, Switzerland[1])

DRUG	PREGNANCY			LACTATION		
	Safety data	**Compatibility**	**Recommendations**	**Level of exposure**	**Compatibility**	**Recommendations**
Azole	Numerous human data for fluconazole and itraconazole; no human data for posaconazole and voriconazole	To be used with caution	Craniofacial, skeletal and cardiac malformations after high dose (400-800 mg daily) and long term therapy with fluconazole have been reported in humans. In the absence of safer alternative, fluconazole and itraconazole can be used for short-term therapy at low dose.	RID >15% for fluconazole	To be used with caution	In the absence of safer alternative, the most documented compounds of the class should be preferred (i.e. fluconazole). Local use is safe for the breastfed infant.
Amphotericin B	Limited human data	To be used with caution	Intravenous use should be reserved for life-threatening infections. Possible placental accumulation. Oral or topical use is acceptable.	RID unknown	Second line treatment in CF lactating patient	Probably limited systemic absorption in the breastfed infant due to poor oral bioavailability. Topical or oral use is safe for the breastfed infant.
Nystatin (topical or oral use)	Limited human data; limited systemic absorption	Drug of choice in CF pregnant patient		RID unknown	Drug of choice in CF pregnant patient	Poor oral bioavailability. Topical or oral use is safe for the breastfed infant.

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Oseltamivir	Numerous human data	Drug of choice in CF pregnant patient	First choice if influenza antiviral therapy is indicated	RID <0.5%	Drug of choice in CF lactating patient	First choice if influenza antiviral therapy is indicated
Acyclovir	Numerous human data	Drug of choice in CF pregnant patient	First choice if systemic antiviral therapy is indicated	RID <7%	Drug of choice in CF lactating patient	RID equivalent to ~ 1% of the recommended infant dosage taking into account poor systemic absorption (20%).
Ganciclovir	Limited human data	Second line treatment in CF pregnant patient	To use only in case of therapeutic advantage over acyclovir, especially during first trimester	RID unknown	To be used with caution	Safety has not been assessed.
Valaciclovir	Limited human data	Drug of choice in CF pregnant patient	Prodrug of acyclovir, safety profile can be considered similar	RID <7%	Drug of choice in CF lactating patient	RID equivalent to ~ 1% of the infant dosage similar as by maternal acyclovir intake.

Table 3: Drugs acting mainly on the respiratory system in pregnant and lactating CF patients (Copyright© 2016 Karger Publishers, Basel, Switzerland[1])

DRUG	PREGNANCY			LACTATION		
	Safety data	**Compatibility**	**Recommendations**	**Level of exposure**	**Compatibility**	**Recommendations**
Inhaled corticosteroids (for systemic use see immunosuppressants)	Numerous human data; limited systemic absorption	Drug of choice in CF pregnant patient	Well-established compounds of the class should be preferred (e.g. budesonide, fluticasone, beclomethasone)	RID <1% for budesonide	Drug of choice in CF lactating patient	Well-established compounds of the class should be preferred (e.g. budesonide)
Inhaled selective beta2-agonists	Numerous human data; limited systemic absorption	Drug of choice in CF pregnant patient	Well-established compounds of the class should be preferred (i.e. salbutamol/albuterol for SABA; salmeterol, formoterol for LABA). Despite limited systemic absorption, a possible systemic effect cannot be ruled out	RID<1%	Drug of choice in CF lactating patient	Well-established compounds of the class should be preferred (i.e. salbutamol/albuterol for SABA; salmeterol, formoterol for LABA).
Inhaled anticholinergics	Limited human data; limited systemic absorption	Second line treatment in CF pregnant patient	Should be used only if safer alternatives are not effective	RID unknown	Second line treatment in CF lactating patient	Well-established compounds of the class should be preferred (e.g. ipratropium)
Leukotriene antagonists	Limited human data	Second line treatment	Should be used only if safer alternatives are not effective	RID unknown	Second line treatment in CF lactating patient	Should be used only if safer alternatives are not effective

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Drugs improving airway clearance	Limited human data; important hindsight	Drug of choice in CF pregnant patient	limited bio-availability for mucolytic agent, hypertonic saline (3-7%), mannitol and dornase alpha	RID unknown	Drug of choice in CF lactating patient	Limited systemic bio-availability for chest physiotherapy agents.
Histamine antagonists	Numerous human data	Drug of choice in CF pregnant patient	Well-established compounds of the class should be preferred (e.g. cetirizine, loratadine).	RID <1% for loratadine and cetirizine	Drug of choice in CF lactating patient	Non-sedative drugs should be preferred (e.g. loratadine, cetirizine) Monitor the suckling infant for restlessness or mild sedation.
Inhaled rhDNase	Limited human data; poor systemic absorption	Drug of choice in CF pregnant patient	Limited systemic absorption. Similar to endogenous compound	RID unknown	Drug of choice in CF lactating patient	Limited systemic absorption
CFTR modulators **- Ivacaftor** **- Lumacaftor/ ivacaftor**	Limited human data	Should be used with caution	Safety has not been assessed	RID unknown	Should be used with caution	Safety has not been assessed

Table 4: Drugs of the gastro-intestinal system in pregnant and lactating CF patients (Copyright© 2016 Karger Publishers, Basel, Switzerland[1])

DRUG	PREGNANCY			LACTATION		
	Safety data	**Compatibility**	**Recommendations**	**Level of exposure**	**Compatibility**	**Recommendations**
Pancreatic enzymes	Limited human data; poor systemic absorption	Drug of choice in CF pregnant patient		RID unknown	Drug of choice in CF lactating patient	Poor systemic absorption.
Antacids	Numerous human data; poor systemic absorption	Drug of choice in CF pregnant patient. **Misoprostol is contraindicated during pregnancy.**	Well-established compounds of the class should be preferred (i.e. omeprazole or esomeprazole for proton pump inhibitors, ranitidine for H2 receptor antagonists). Misoprostol has abortive properties and is linked to an increased risk of Moebius sequence.	RID unknown for magnesium or aluminum salts RID >5% for H2-blockers RID <2% for proton pump inhibitors	Drug of choice in CF lactating patient.	The most documented compounds of the class should be preferred (i.e. omeprazole, esomeprazole for proton pump inhibitors, ranitidine for H2 receptor antagonists).
Prokinetics	Numerous human data for metoclopramide; limited human data for domperidone	Drug of choice in CF pregnant patient (metoclopramide)	Metoclopramide should be preferred in first trimester.	RID <2% for domperidone RID 5-15% for metoclopramide	Drug of choice in CF lactating patient (metoclopramide)	

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Laxatives	Limited human data; important hindsight; poor systemic absorption	Drug of choice in CF pregnant patient	Limited systemic absorption for most laxatives. Use of anthraquinones should be limited to short periods in case of refractory constipation. Long term use of mineral oil should be avoided during pregnancy.	RID unknown	Drug of choice in CF lactating patient	Limited systemic absorption for most laxatives. Bulking agents and osmotic laxatives should be preferred. Short time use of senna preparations (i.e. containing anthraquinones) and mineral oil is acceptable.
Anti-diabetics	Numerous human data for insulin; limited human data for oral antidiabetics	Drug of choice in CF pregnant patient (Insulin)	Poor control of blood sugar level during pregnancy is correlated with pre- and post-natal developmental impairment (e.g. increased rate of congenital malformation, macrosomia, neonatal hypoglycemia) Insulin has no placental transfer and should be preferred. Metformin can be considered during the second and third trimester.	RID <2% for metformin	Drug of choice in CF pregnant patient (Insulin)	Insulin and metformin should be preferred.

Ursodeoxycholic acid	Limited human data	To be used with caution	Avoid during the first trimester.	RID unknown	Drug of choice in CF lactating patient	Only trace amounts in the maternal plasma.
Biphosphonates	Limited human data	To be used with caution	Avoid in pregnancy.	RID unknown	To be used with caution	Avoid during breastfeeding even if adverse effect is not expected. If used, no breastfeeding during the peak plasma time (e.g. 2 hours for alendronate).
Vitamins	Important hindsight	Drug of choice in CF pregnant patient	Except for vitamin A, vitamin deficiency should be compensated accordingly to laboratory normal values. For vitamin A, doses ≤ 10'000 IU are considered safe.	Important hindsight	Drug of choice in CF pregnant patient	Any vitamin deficiency should be addressed.

Table 5: Anti-inflammatory drugs in pregnant and lactating CF patients (Copyright© 2016 Karger Publishers, Basel, Switzerland[1])

DRUG	PREGNANCY			LACTATION		
	Safety data	Compatibility	Recommendations	Level of exposure	Compatibility	Recommendations
Corticosteroids (for inhaled use see respiratory system)	Numerous human data	Drug of choice in CF pregnant patient	Well-established compounds of the class should be preferred (e.g. prednisone, prednisolone)	RID <2% for prednisone and prednisolone	Drug of choice in CF lactating patient	Well-established compounds of the class should be preferred (e.g. prednisone, prednisolone)
NSAIDs	Numerous human data	To be used with caution	NSAIDs can lead to fetal nephrotoxic effects after the 12th week of pregnancy and to premature closure of the fetal ductus arteriosus after the 28th week. Occasional use is acceptable during the second trimester. Avoid during the third trimester. Well-established compounds of the class should be preferred (e.g. ibuprofen).	RID <1% for ibuprofen	Drug of choice in CF lactating patient	Most documented compounds of the class should be preferred (e.g. ibuprofen).

Table 6: Vaccines in pregnant and lactating CF patients (Copyright© 2016 Karger Publishers, Basel, Switzerland[1])

DRUG	PREGNANCY			LACTATION		
	Safety data	**Compatibility**	**Recommendations**	**Level of exposure**	**Compatibility**	**Recommendations**
Inactivated vaccines	Numerous human data	Drug of choice in CF pregnant patient	Before pregnancy, update routine adult vaccines. During flu season, pregnant women should be immunized against influenza, even during the first trimester.	NA	Drug of choice in CF lactating patient	Breastfeeding women may be immunized with inactivated vaccines using standard recommended doses for adults.
Live attenuated vaccines	Limited human data	To be used with caution	Theoretical concern about fetal infection	NA	Drug of choice in CF lactating patient	Breastfeeding women may be immunized with live attenuated vaccines using standard recommended doses for adults.

7. REFERENCES

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