Safety of Drugs during Pregnancy and Breastfeeding in Cystic Fibrosis Patients

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Key Words

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Abstract

Health management of cystic fibrosis (CF) patients should be maximized during pregnancy and breastfeeding because of its significant impact on the maternal and newborn outcomes. Thus, numerous drugs will have to be continued during pregnancy and lactation. Most of the drugs representing CF treatment lines cross the placenta or are excreted into human milk. Research addressing the risks and benefits of drugs used in CF patients during pregnancy and lactation is often incomplete or challenged by limited methodology, which often leads to conflicting or inconclusive results. Yet, potential treatment benefits for CF pregnant patients most often outbalance potential risks for the unborn child.

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Introduction

Median survival of patients suffering from cystic fibrosis (CF) has dramatically improved over the last decades, due to treatment and nutrition optimization. With increasing life expectancy, more and more women with CF wish to conceive. In contrast to males, the majority of females with CF have near-normal fertility, despite possible ovulation disturbances in patients with more severe disease [1].

About 240 pregnancies in CF patients are reported annually to the US Cystic Fibrosis Foundation Registry [2]. Furthermore, data from the US Nationwide Inpatient Sample showed a significant linear increase in the number of women with CF at delivery, going from 2.99 to 9.84 per 100,000 deliveries over the 2000–2010 period [3]. Proposed prognostic markers for pregnancy and fetal outcomes are lung function parameters (before and during pregnancy), overall nutritional status, CF-related diabetes and post-lung transplantation status [4–6]. Several studies have reported favorable maternofetal outcomes during and following pregnancy in women with CF,

whereas others described adverse outcomes. According to Patel et al. [7], women with CF are at increased risk of death, infectious morbidity, acute renal failure, preterm labor among other obstetric complications and require more mechanical ventilation. While pregnancy and motherhood do not appear to accelerate disease progression up to 11 years after pregnancy, they are linked to a higher frequency of illness-related medical visits, pulmonary exacerbations, and a decrease in some domains of quality of life [3].

CF is a multisystem disease that affects primarily the respiratory and the digestive systems, and most patients require chest physiotherapy, nutritional supplements, pancreatic enzymes, mucolytics, long-term oral and nebulized antibiotics [8], frequent courses of intravenous antibiotics and immunosuppressive drugs after transplantation, most of which will have to be continued during pregnancy. Because of its significant impact on obstetrical and neonatal outcomes, health management of CF patients should be maximized and should include preconceptually an accurate medication review for the reassessment of each medication safety and effectiveness in the light of the upcoming pregnancy. This review offers an evaluation of up-to-date safety data during pregnancy and lactation of the most current drugs used in CF patients, providing healthcare professionals with a comprehensive review for decision making.

Drugs in Pregnancy and Breastfeeding

Drugs can interfere with a variety of developmental and reproductive processes causing infertility, chromosomal and genetic disorders, spontaneous abortions, intrauterine deaths, prematurity, low birth weight, birth defects and functional disorders [9]. Most drugs have a low molecular weight (600–800 Da) and are therefore able to cross the placenta. Organogenesis, which takes place between 20 and 70 days after the first day of the last menstruation period, is the critical period for the induction of structural malformations [9]. During the fetal period, drugs can induce growth restriction, some forms of structural malformations, fetal death, functional impairment, and transplacental carcinogenesis [9]. Prenatal and early postnatal exposure to drugs can lead to behavioral, reproductive, endocrine, immune, and various other physiological function impairments [9]. Drug exposure through human breast milk rarely achieves significant doses in the infant, and interferences will depend on the infant's ability to eliminate the drug and infant's sensitivity to the

pharmacological effects [10]. The clinically most relevant parameter available to evaluate the level of drug exposure of the infant through breast milk is the relative infant dose (RID). RID is a weight-normalized parameter calculated by dividing the dose of drug ingested via milk (mg/kg/day) by the mother's dose in mg/kg/day.

The evaluation of risks and benefits of drugs during pregnancy and lactation is often incomplete. It is most often based on case reports, case series and cohort studies, while evidence-based randomized controlled trials are rarely used in pregnant and lactating women, mainly for ethical reasons. Furthermore, the low prevalence of most of the drug-related risks requires very large sample sizes to formally establish the safety of a drug during pregnancy or lactation, which are often not available. This situation frequently leads to conflicting or inconclusive information making therapeutic decisions difficult for clinicians.

Drugs Used in CF Patients

Respiratory System

Pulmonary manifestations remain the major cause of morbidity and mortality in CF patients. Infection control, improvement of airway clearance, and bronchodilation are the cornerstones of CF management [11].

Antibiotics

Pregnancy. Antibiotics are the major components of CF treatment and are administered chronically (e.g. inhaled antibiotics, macrolides used for their immunomodulatory properties) or intermittently to prevent, eradicate, control or treat respiratory infections [12, 13]. Due to increased antibiotic clearance and distribution, higher doses are usually administered to CF patients, and a combination of antibiotics is often necessary due to the presence of multiple or multiresistant microorganisms.

Most antibiotics are safe for use in pregnancy (table 1). All the antibiotics for which the placental transfer has been studied can be detected in the amniotic fluid [14]. Penicillins, well-documented cephalosporins (e.g. cefaclor, cefuroxime, ceftriaxone) and macrolides (azithromycin, clarithromycin, erythromycin) are first-line treatments during pregnancy for sensible pathogens such as *Staphylococcus aureus* or *Haemophilus influenzae* [9, 15–17]. Antipseudomonal penicillins, including piperacillin, piperacillin-tazobactam, temocillin, and less documented cephalosporins (ceftazidime, cefepime), carbapenems (meropenem, imipenem, ertapenem), monobactam (az-

Table 1. Antibiotics in pregnant and lactating CF patients

Drug	Pregnancy			Lactation		
	safety data	compatibility	recommendations	level of exposure	compatibility	recommendations
Penicillins	Numerous human data	Drug of choice in pregnant CF patients	If necessary, combination therapy with a betalactamase inhibitor can be used (e.g. clavulanic acid, tazobactam)	RID <2%	Drug of choice in lactating CF patients	Intravenous use often linked to poor oral bioavailability and subsequent systemic exposure in the suckling infant May alter gastrointestinal flora of the suckling infant
Cephalosporins	Numerous human data	Drug of choice in pregnant CF patients	If equally effective, well-established compounds of the class should be preferred (e.g. cefaclor, cefuroxim, ceftriaxon)	RID <2%	Drug of choice in lactating CF patients	Intravenous use often linked to poor oral bioavailability and subsequent systemic exposure in the suckling infant May alter gastrointestinal flora of the suckling infant
Carbapenems	Limited human data	Second-line treatment in pregnant CF patients	Imipenem and meropenems should be used only in the absence of a safer alternative	RID <2%	Second-line treatment in lactating CF patients	Poor oral bioavailability and subsequent systemic exposure in the suckling infant If effective, the most documented compounds of the class should be preferred (e.g. imipenem)
Mono-bactam	Limited human data	Second line treatment in pregnant CF patients	Aztreonam should be used only in the absence of a safer alternative	RID <2%	Second-line treatment in lactating CF patients	Poor oral bioavailability
Macrolides	Numerous human data for azithromycin, clarithromycin, erythromycin	Drug of choice in pregnant CF patients	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 lactating CF patients	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 pregnant CF patients	Norfloxacin and ciprofloxacin can be used in the absence of a safer alternative	RID >5%	Second-line treatment in lactating CF patients	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 nephrotoxicity 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 lactating CF patients	Poor oral bioavailability After intravenous use, avoid breastfeeding during the 2 h 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)

Table 1 (continued)

Drug	Pregnancy			Lactation		
	safety data	compatibility	recommendations	level of exposure	compatibility	recommendations
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 lactating CF patients	Inhaled colistin is safe for the breastfed infant
Sulfonamides	Numerous human data	Second-line treatment in pregnant CF patients	During the first trimester, high dose or long-term use of sulfonamides, such as sulfamethoxazol-trimethoprim combined with a folate antagonist (e.g. trimethoprim) should be associated with folic acid intake (1–5 mg/day), even though evidence is lacking to support its efficacy Sulfonamide use until birth can be associated with a rise in bilirubin, especially in premature neonates	RID >5% for trimethoprim	Second-line treatment in lactating CF patients	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 pregnant CF patients	Should be used only in the absence of a safer alternative	RID <2%	Second-line treatment in lactating CF patients	Should be used only in the absence of a safer alternative

treonam), can be safely used intravenously for *Pseudomonas* exacerbation.

Clindamycin, sulfonamides, trimethoprim, and cotrimoxazole are antibiotics of second choice in pregnancy, and can be used when first-line antibiotics are ineffective or in case of allergy [9, 15]. In case of long-term first-trimester use of sulfonamides with a folate antagonist (e.g. trimethoprim), increased folic acid intake (1–5 mg/day) is recommended, even though evidence is lacking to support its efficacy in preventing teratogenic effects [9, 17]. When sulfonamides are used until birth, a rise in bilirubin may be observed, especially in premature infants [9]. Tetracyclines have not been associated with an increased risk of malformations [18]. However, they can cause tooth discoloration and inhibition of bone growth if used after the 15th week of pregnancy due to binding to calcium ions [9, 15, 17]. Aminoglycosides carry a small risk of fetal nephro- and ototoxicity [9, 17, 19]. Therefore, their intravenous use should be reserved for life-threatening infections. Dose adjustment by therapeutic drug monitoring in pregnant CF patients is recommended with gentamicin, amikacin and tobramycin for efficacy and safety optimization in pregnancy [20].

Inhaled tobramycin is associated with minimal risks because of the limited systemic absorption. Quinolones have been associated with irreversible damage of joint

cartilages in young animals treated directly (i.e. none resulting from in utero exposure). This has never been observed after in utero exposure to quinolones in humans [18, 21, 22]. In the absence of alternatives, the well-documented norfloxacin and ciprofloxacin should be preferred. Because of the lack of security data in pregnancy, intravenous colistin should be reserved for life-threatening infections, while its limited systemic absorption after inhalation limits the risks [9].

Breastfeeding. Most antibiotics are excreted into breast milk in very small amounts (table 1). A transient effect on the infants' stool consistency is the most frequently observed adverse event in infants exposed to antibiotics via breast milk [23]. Antibiotics discussed below are compatible with breastfeeding. Penicillins, cephalosporins and macrolides are first-line treatments during lactation [9, 17]. A short-time therapy with tetracyclines is possible (<3 weeks), while clindamycin, sulfonamides, colistin and quinolones should only be used in CF lactating women when first-line antibiotics are ineffective. As a result of their poor oral bioavailability, carbapenems, monobactams or aminoglycosides are probably safe for the breastfed infant after maternal intravenous administration. Inhaled use of antibiotics is compatible with breastfeeding [24].

Table 2. Antifungal and antiviral agents in pregnant and lactating CF patients

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 lactating CF patients	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 pregnant CF patients		RID unknown	Drug of choice in pregnant CF patients	Poor oral bioavailability Topical or oral use is safe for the breastfed infant
Oseltamivir	Numerous human data	Drug of choice in pregnant CF patients	First choice if influenza antiviral therapy is indicated	RID <0.5%	Drug of choice in lactating CF patients	First choice if influenza antiviral therapy is indicated

Antifungals

Although invasive fungal infections are infrequent in the nontransplanted CF patients, sensitization to fungi and notably to aspergillus may lead to allergic bronchopulmonary aspergillosis. The latter necessitates treatment with systemic corticosteroids, which may be combined with antifungal agents [25].

Pregnancy. In animal studies, azole antifungals cross the placenta and are teratogenic at high doses (table 2). Craniofacial, skeletal, and cardiac malformations, similar to those observed in animal studies, have been described after first trimester use of prolonged high doses of fluconazole (400–800 mg daily) [26–28]. However, low-dosage regimens have not been associated with an increased birth defect risk in various studies including several thousand first trimester exposures to fluconazole [29, 30]. Likewise, itraconazole has not been associated with an increased birth defect risk according to prospective studies including several hundred first trimester exposures [31]. Human data are lacking for voriconazole and posaconazole. Based on current data, azole derivatives should be used with caution when administered systemically, at least during the first trimester of pregnancy. Fluconazole

and itraconazole are to be preferred as the best investigated drugs.

Amphotericin B crosses the placenta, and the limited human data do not allow for an adequate risk assessment (table 2). The systemic use of amphotericin B should be reserved for life-threatening infections [9]. Liposomal amphotericin B should be preferred to reduce the risk of nephrotoxicity and oral or local use is acceptable during pregnancy as systemic absorption is minimal.

Oral nystatin is poorly absorbed and has not been associated with an increased risk of birth defect [32] (table 2).

Breastfeeding. Fluconazole is transferred into human breast milk, resulting in an RID equivalent to 5% of the usual pediatric dose (6 mg/kg/day) [10, 33]. Fluconazole is associated with a good safety profile in pediatric patients. Although data on the systemic use of itraconazole, posaconazole and voriconazole are unavailable [9, 10], breastfeeding interruption is not justified, but their use should be reserved for situations requiring a systemic use (table 2). The best-investigated compound fluconazole and nystatin for local infections should be preferred whenever possible. Even if no data are available for am-

photericin in breastfeeding, its use is probably associated with a limited risk due to its poor oral bioavailability [10].

Antivirals

Respiratory viral infections may lead to prolonged symptoms and may worsen the course of CF. Despite a paucity of studies in this context, it is considered that neuraminidase inhibitors against influenza infection may be helpful in limiting clinical manifestations [34].

Pregnancy. No evidence of embryo- or fetotoxic risks has been reported for oseltamivir in more than several hundred documented exposures [35–39]. Oseltamivir is considered a first choice in influenza treatment during pregnancy [9] (table 2).

Breastfeeding. Oseltamivir is transferred into human milk in limited amounts, with an RID of <0.5 [10] (table 2).

Inhaled Corticosteroids

Pregnancy. Safety of inhaled corticosteroids (ICS) during pregnancy is well-established (e.g. several thousand documented pregnancy exposures for budesonide) and the vast majority of studies did not report any increased risk of birth defects or adverse perinatal outcomes associated with ICS use [40–47]. An increased overall malformation rate in infants exposed to high-dose ICS treatments (>1,000 µg/day of beclomethasone dipropionate-chlorofluorocarbon equivalent) was suggested [48]. However, these studies did not account for the indication as an important confounding factor (e.g. asthma severity) [41] and results have not been confirmed in other large cohort studies or meta-analyses [41, 44, 46, 49, 50]. Data on long-term ICS use during pregnancy and the incidence of pediatric diseases in the exposed offspring are scarce but mostly reassuring [50]. Even though fluticasone and beclomethasone are not as well documented as budesonide, both show a similar safety profile [50]. ICS are considered to be safe during pregnancy and can be continued in CF patients if needed (table 3).

Breastfeeding. A small study of 8 women treated by inhaled budesonide during lactation reported an RID of <1% [51]. Exposed infants had undetectable serum budesonide concentrations. There are no available data on the excretion of other ICS into breast milk. Based on these results and on the limited systemic absorption, ICS are considered compatible with breastfeeding (table 3).

Inhaled β_2 -Agonists

Pregnancy. Inhaled β_2 -agonists are divided into short-acting (SABA; e.g. salbutamol/albuterol, terbutaline) and long-acting bronchodilators (LABA, e.g. salmeterol, for-

moterol). A few studies found a slightly increased risk of all congenital malformations [52] or specific birth defects such as gastroschisis [53], heart defects [52, 54], cleft lip [55], esophageal atresia [47], anorectal atresia [47], or omphalocele [47] after exposure to a SABA (e.g. salbutamol/albuterol, terbutaline). However, results from a recent meta-analysis suggest that these associations may be chance findings or related to the underlying asthma severity [41]. In contrast, no increase in malformation rate was reported by large database studies [44, 50, 56, 57]. Several studies support the absence of obstetrical or perinatal complications associated with SABA use [44, 58–60]. There are limited observational data on the safety of LABA during pregnancy, although an increase in cardiac malformations has been reported in one study [56]. No difference in perinatal risks has been reported between salmeterol and formoterol [61]. Even if systemic absorption of inhaled β_2 -agonists is generally low, a systemic effect on mother and fetus cannot be formally excluded (e.g. tachycardia, arrhythmia, glucose intolerance, inhibition of uterine contractions). Patients requiring a SABA or LABA to control asthmatic symptoms should be encouraged to continue treatment during pregnancy. The best investigated drugs should be preferred (i.e. salbutamol/albuterol for SABA; salmeterol or formoterol for LABA; table 3).

Breastfeeding. No published data exist on the use of inhaled β_2 -agonists during lactation. Based on the limited systemic absorption after administration by inhalation, inhaled β_2 -agonists are considered compatible with breastfeeding, and patients should be encouraged to continue inhaled β_2 -agonists during breastfeeding (table 3).

Inhaled Anticholinergics

Pregnancy. Inhaled anticholinergics such as ipratropium are not teratogenic in animals, but well-controlled studies in humans are lacking. One case of renal obstruction was observed out of 37 infants born to women who took ipratropium during pregnancy [62]. Even if systemic absorption is limited, inhaled anticholinergics should only be used if first-line therapies are not effective (e.g. SABA, LABA, ICS; table 3).

Breastfeeding. No data on the safety of inhaled anticholinergics in breastfeeding are available, but excreted amounts of drug are likely to be negligible due to limited systemic absorption (table 3).

Drugs Improving Airway Clearance

Pregnancy. No data on mucolytic agents, hypertonic saline (3–7%), and mannitol use during pregnancy are available, and therefore proper risk assessment is not pos-

Table 3. Drugs acting on the respiratory system in pregnant and lactating CF patients

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 pregnant CF patients	Well-established compounds of the class should be preferred (e.g. budesonide, fluticasone, beclomethasone)	RID <1% for budesonide	Drug of choice in lactating CF patients	Well-established compounds of the class should be preferred (e.g. budesonide)
Inhaled selective β_2 -agonists	Numerous human data; limited systemic absorption	Drug of choice in pregnant CF patients	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 lactating CF patients	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 pregnant CF patients	Should be used only if safer alternatives are not effective	RID unknown	Second-line treatment in lactating CF patients	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 lactating CF patients	Should be used only if safer alternatives are not effective
Drugs improving airway clearance	Limited human data; important hindsight	Drug of choice in pregnant CF patients	limited bioavailability for mucolytic agents, hypertonic saline (3–7%) and mannitol	RID unknown	Drug of choice in lactating CF patients	Limited systemic bioavailability for mucolytic agents, hypertonic saline (3–7%) and mannitol
CFTR modulators	No human data	Should be used with caution	Safety has not been assessed	RID unknown	Should be used with caution	Safety has not been assessed
Inhaled rhDNase	Limited human data; poor systemic absorption	Drug of choice in pregnant CF patients	Limited systemic absorption. Similar to endogenous compound	RID unknown	Drug of choice in lactating CF patients	Limited systemic absorption

sible to date. However, as those preparations have a limited systemic absorption when administered by inhalation, no fetal adverse effects are expected (table 3).

Clinical experience with dornase alfa, a human recombinant deoxyribonuclease I, is relatively small, and therefore human studies in pregnancy are lacking. Due to the presence of endogenous DNase in human serum and the poor systemic absorption of inhaled dornase alfa, this medication may be used in pregnant CF women if needed (table 3).

Breastfeeding. Excretion of mucolytic agents such as N-acetylcysteine and hypertonic saline into breast milk has not been investigated. Considering their general safety profile and limited absorption after inhalation, the use

of these compounds is probably safe for the breastfed infant (table 3).

Studies investigating dornase alfa safety during lactation are lacking. Since it is a large protein poorly absorbed after inhalation, excretion into breast milk should be low and is not expected to cause any adverse effects in breastfed infants (table 3).

Leukotriene Antagonists

Pregnancy. Leukotriene antagonists have been used in CF for their anti-inflammatory properties [63]. Limited human data exist on the safety of leukotriene antagonists during pregnancy. According to the manufacturer pregnancy registry including several hundreds of patients, 19

cases of congenital anomalies were reported until July 2009 with montelukast [62]. Limb reduction defects were present in 6 montelukast-exposed children, but this association was not confirmed in a large database study [64] or in 3 other studies that did not report any increase in perinatal complications or congenital malformations [65, 66]. Leukotriene antagonists should be considered as a second-line treatment during pregnancy, and, when needed, the best investigated leukotriene antagonist montelukast should be preferred (table 3).

Breastfeeding. No published information is available on the use of leukotriene antagonists during lactation. Data on zafirlukast suggest that only small amounts are excreted into human breast milk (probably RID <1%) [67]. Due to limited experience, leukotriene antagonists should only be used during breastfeeding when alternative antiasthmatic drugs are not effective (table 3).

CF Transmembrane Conductance Regulator Modulators

Pregnancy. Drugs modulating CF transmembrane conductance regulator (CFTR) dysfunction have been the focus of research during the recent years. Ivacaftor and combination of ivacaftor/lumacaftor have been licensed, respectively, for patients who have one gating CFTR mutations [68] and patients homozygous for the F508del mutation [69]. Clinical experience with ivacaftor/lumacaftor is relatively small, and human studies investigating drug safety during pregnancy are lacking. Ivacaftor/lumacaftor should be used with caution in pregnant CF patients until more clinical data are available (table 3).

Breastfeeding. Due to the lack of data of ivacaftor and ivacaftor/lumacaftor excretion into breast milk, it should better not be used during breastfeeding (table 3).

Gastrointestinal System

CF digestive system manifestations are diverse and may include pancreatic insufficiency, acute or chronic pancreatitis, liver cirrhosis, chronic constipation, distal intestinal obstruction syndrome, gastroesophageal reflux disease, esophageal dysmotility, and cholestasis [70]. Pancreatic insufficiency predisposes to fat-soluble vitamin deficiency and may lead to additional manifestations, such as decreased bone mineral density due to vitamin D or K deficiency. CF-related diabetes occurrence increases with age, affecting almost 50% of patients after 40 years.

Pancreatic Enzymes

Pregnancy. No data of pancreatic enzyme use during pregnancy are available, and therefore proper risk assess-

ment is not possible to date. As those preparations have a very limited systemic absorption, no fetal adverse effects are expected [9] (table 4).

Breastfeeding. Pancreatic enzymes can be considered compatible with breastfeeding (table 4) due to their limited absorption [10, 67].

Antacids

Pregnancy. Antacids may be used throughout pregnancy. Fixed combinations of aluminum and magnesium salts should be preferred and used at recommended doses. No associations with an increased rate of birth defects have been detected after more than 1,500 exposures during the first trimester with ranitidine [71, 72]. No associations have been found between proton pump inhibitor use during pregnancy and increased rate of birth defects in studies including several thousands of patients [73, 74]. Omeprazole, the best investigated proton pump inhibitor to date, and its enantiomer esomeprazole are the medication of choice. Misoprostol has an uterotonic activity and is linked to an increased risk of Moebius sequence. It is contraindicated during pregnancy except for specific obstetrical indications (table 4).

Breastfeeding. Antacids can be used during breastfeeding. Ranitidine reaches variable concentrations in the mother's milk, corresponding however to smaller amounts than the usual pediatric dosage. Omeprazole and esomeprazole are acid labile compounds and are likely to be destroyed in the infant's stomach prior to systemic absorption. Based on these considerations, antacids are not expected to cause adverse effects in breastfed infants (table 4).

Prokinetics

Pregnancy. Metoclopramide has been widely used in the treatment of nausea and vomiting in pregnancy, and safety data are numerous for this compound [75, 76]. It is considered as the antiemetic of choice during pregnancy [9] (table 4). Domperidone is not a drug of choice in pregnancy as its safety has only been demonstrated in a small study.

Breastfeeding. Metoclopramide and domperidone are excreted in small amounts into breast milk [77, 78] with no adverse events reported in breastfed infants. If both prokinetics may be used during breastfeeding, domperidone is excreted in smaller amounts into milk and is less able to cross the infant blood-brain barrier (table 4).

Laxatives

Pregnancy. Bulking agents characterized by a high content of cellulose and derivatives, osmotic laxatives

Table 4. Drugs acting on the gastrointestinal system in CF pregnant and lactating patients

Drug	Pregnancy			Lactation		
	safety data	compatibility	recommendations	level of exposure	compatibility	recommendations
Pancreatic enzymes	Limited human data; poor systemic absorption	Drug of choice in pregnant CF patients		RID unknown	Drug of choice in lactating CF patients	Poor systemic absorption
Antacids	Numerous human data; poor systemic absorption	Drug of choice in pregnant CF patients 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 lactating CF patients	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 pregnant CF patients (metoclopramide)	Metoclopramide should be preferred in the first trimester	RID <2% for domperidone RID 5–15% for metoclopramide	Drug of choice in lactating CF patients (metoclopramide)	
Laxatives	Limited human data; important hindsight; poor systemic absorption	Drug of choice in pregnant CF patients	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 lactating CF patients	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
Antidiabetics	Numerous human data for insulin; limited human data for oral antidiabetics	Drug of choice in pregnant CF patients (insulin)	Poor control of blood sugar level during pregnancy is correlated with pre- and postnatal 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 trimesters	RID <2% for metformin	Drug of choice in pregnant CF patients (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 lactating CF patients	Only trace amounts in the maternal plasma
Bisphosphonates	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 h for alendronate)
Vitamins	Important hindsight	Drug of choice in pregnant CF patients	Except for vitamin A, vitamin deficiency should be compensated according to laboratory normal values For vitamin A, doses ≤10,000 IU are considered safe	Important hindsight	Drug of choice in pregnant CF patients	Any vitamin deficiency should be addressed

such as lactulose, lactitol, macrogol (without electrolytes), and glycerol used rectally are nonabsorbable laxatives. These are considered to be safe during pregnancy and should be used as first-line agents. A stimulation effect in the uterine musculature and an in utero meconium release cannot be ruled out with anthraquinone-based preparations (e.g. senna). Chronic use of mineral oil may interfere with the absorption of fat-soluble vitamins and be the cause of lipoid pneumonia after aspiration. Therefore, the use of anthraquinone-based preparations and mineral oil should be limited to short periods in case of refractory constipation (table 4). There is no human data regarding the reproductive safety of prucalopride, which does not allow a proper risk assessment. Thus, this drug should be avoided during the first trimester of pregnancy.

Breastfeeding. The use of bulking agents and osmotic laxatives is probably safe for the breastfed infant owing to their nonabsorbable properties [9]. A risk of diarrhea in the breastfed infant cannot be excluded with anthraquinone-based preparations (table 4). There are no human data regarding the safety of prucalopride, and this drug should thus be avoided during breastfeeding.

Ursodeoxycholic Acid (Ursodiol)

Pregnancy. Ursodeoxycholic acid improves bile flow and is used in patients presenting CF-related liver disease. It is also used in the management of gestational cholestasis in the second and third trimester in non-CF patients. No malformations have been reported, but the scarce data do not allow a proper risk assessment. Thus, this drug should be avoided during the first trimester of pregnancy (table 4). [79].

Breastfeeding. Ursodeoxycholic acid is not excreted in significant amounts into milk [80, 81]. When indicated, its use is acceptable during breastfeeding (table 4).

Bisphosphonate

Pregnancy. No malformations have been reported after exposure to bisphosphonate in humans, the scarce data available do not allow a proper risk assessment though. Thus, this drug class should be avoided during pregnancy (table 4).

Breastfeeding. Based on their limited systemic absorption, the use of these compounds is probably safe for the breastfed infant [9]. If a bisphosphonate is used during breastfeeding, the infant should not be breastfed during the peak plasma time (e.g. 2 h for alendronate).

Antidiabetics

Pregnancy. Poor control of blood sugar level during pregnancy is correlated with adverse pregnancy (e.g. increased rate of congenital malformation and miscarriage, macrosomia, hydramnios, traumatic birth) and neonatal outcomes (e.g. neonatal hypoglycemia, brachial plexus injury) [82]. Therefore, maintaining euglycemia throughout pregnancy is essential. Insulin has no placental transfer and is considered first-line treatment in diabetes during pregnancy. Human data are limited regarding the reproductive safety of oral antidiabetics. Recent studies investigating metformin safety did not show an increased rate of birth defects, when used to treat insulin resistance in women with polycystic ovarian syndrome [83]. However, available data do not allow an accurate risk assessment, and larger studies are warranted in order to confirm safety and efficacy of this drug during the first trimester. If insulin cannot be used, metformin is a possible alternative during the second and third trimesters (table 4).

Breastfeeding. Insulin is a large peptide that is not excreted in significant amounts into breast milk and has very poor systemic absorption after milk ingestion [84]. New insulin analogues also seem to be safe during lactation. Only small amounts of metformin are found in the mother's milk and no adverse events have been reported in breastfed infants [85, 86]. Insulin and metformin are considered as safe during breastfeeding (table 4).

Vitamins

Pregnancy. Approximately 85% of CF patients present exocrine pancreatic insufficiency, which predisposes to an impaired absorption of fat-soluble vitamins. Adequate nutritional status has to be maintained throughout pregnancy (table 4). Serum levels of vitamins that are at high risk of deficiency [i.e. fat-soluble vitamins (A, D, E, K) and vitamin B₁₂] should be closely monitored. A teratogenic effect similar to retinoids has been associated with high doses of vitamin A (>25,000 UI). This risk has not been confirmed in a large cohort study evaluating the risk of high doses of vitamin A. A daily dose of <10,000 UI is considered safe [87]. Supplementation with folic acid (0.4–0.8 mg daily) should be started in women planning pregnancy and continued throughout the first trimester for the prevention of neural tube defects [88].

Breastfeeding. Adequate nutritional status has to be maintained in CF patients throughout lactation (table 4). Serum levels of vitamins that are at high risk of deficiency [i.e. fat-soluble vitamins A, D, E, K) and vitamin B₁₂] should be closely monitored.

Table 5. Immunosuppressants in pregnant and lactating CF patients

Drug	Pregnancy			Lactation		
	safety data	compatibility	recommendations	level of exposure	compatibility	recommendations
Cyclosporine	Numerous human data	Drug of choice in pregnant CF patients		RID <3%	To be used with caution	Breastfeeding is possible in healthy infants Closely monitor the suckling infant Monitoring can include infant plasma concentration determination
Mycophenolate	Limited human data	Drug contra-indicated during pregnancy	Mycophenolate is teratogenic with a specific pattern of birth defects (microtia and atresia of the external ear, cleft lip, heart defect)	RID unknown	Drug contra-indicated during breastfeeding	Avoid during breastfeeding
Tacrolimus	Limited human data	Second-line treatment in pregnant CF patients	Can be used in the absence of a safer alternative	RID <1%	To be used with caution	Breastfeeding is possible in healthy infants Closely monitor the suckling infant Monitoring can include infant plasma concentration determination
Corticosteroids (for inhaled use, see respiratory system)	Numerous human data	Drug of choice in pregnant CF patients	Well-established compounds of the class should be preferred (e.g. prednisone, prednisolone)	RID <2% for prednisone and prednisolone	Drug of choice in lactating CF patients	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 lactating CF patients	Most documented compounds of the class should be preferred (e.g. ibuprofen)

Immunosuppressants and Anti-Inflammatory Drugs Pregnancy

Nonsteroidal anti-inflammatory drugs (NSAIDs) may modulate lung inflammation of CF or may be used in the context of CF-related arthritis [89]. NSAIDs can be used during the first trimester of pregnancy at usual dosage, and ibuprofen is the drug of first choice (table 5). Even though some retrospective studies observed an increased risk for cardiac defects, oral clefts and gastroschisis after NSAID use during the first trimester [75, 90, 91], overall data on a large number (~10,000) of exposed patients do not suggest a significant increase in birth defect risk [92–94]. In some studies, early use of NSAIDs in pregnancy has been associated with an increased risk of miscarriage [60, 95], which was not confirmed by other studies [96,

97]. Long-term treatment with NSAIDs later in pregnancy is associated with a risk of oligohydramnios. NSAID use during the third trimester of pregnancy (after 28th week of gestation) is contraindicated due to risk of premature closure of the ductus arteriosus, potentially associated with pulmonary hypertension.

CF patients may also require corticosteroids during allergic bronchopulmonary aspergillosis treatment or pulmonary exacerbation. Prednisone and prednisolone are the glucocorticoids of choice for systemic use during pregnancy. They cross the placenta in low concentrations. A meta-analysis found a 3.4-fold increased risk of cleft palate in exposed human fetuses [98]. Several more recently published studies did however not confirm this risk [99–101]. After long-term maternal treatment with high doses of glu-

cocorticoids during the second and third trimesters, an increased risk of intrauterine growth retardation, premature birth, transient hypoglycemia, hypotension, and electrolyte disturbances in the newborn has been observed.

CF patients receive long-term immunosuppressive regimens after lung transplantation. Medication commonly used in this context includes cyclosporine, mycophenolate, tacrolimus and corticosteroids. Cyclosporine is one of the best-studied immunosuppressants during pregnancy. While tacrolimus is also compatible with pregnancy, mycophenolate should be avoided (table 5). Cyclosporine and tacrolimus cross the placenta, and fetal levels reach 30–64 and 23% of maternal plasma concentration, respectively [102–105]. Data on a large number of pregnancies exposed to cyclosporine have not shown a significant increase in major birth defect risk [106–108]. There are less data available on tacrolimus use during pregnancy; however, more than 200 pregnancies have been documented, indicating no teratogenic risk [109–113]. An increased risk of fetal growth restriction, preterm delivery, and preeclampsia has been observed in pregnancies exposed to cyclosporine and tacrolimus [108, 113, 114]. However, underlying medical condition and concomitant drug exposure may also have played a role in this outcome. One study observed a difference in the development or maturation of several cellular components of the immune system in children exposed to cyclosporine during pregnancy compared to nonexposed controls, although no signs of immunodeficiency were evident [115]. Other studies did not show a significant immunosuppressive effect of cyclosporine and other immunosuppressants in children exposed during pregnancy [116, 117]. Decreased kidney function and hyperkalemia have been observed in neonates exposed to tacrolimus throughout pregnancy [113, 118]. Two studies on long-term effects of in utero exposure to cyclosporine did not reveal any anomalies in renal function or cognitive and neurobehavioral development [119, 120].

Mycophenolate use during pregnancy is associated with increased miscarriage and major birth defect risks (table 5). The characteristic mycophenolate embryopathy consists of malformations of the ear (i.e. microtia, atresia of the external ear), craniofacial malformations (i.e. cleft lip and/or palate, micrognathia), ocular malformations (i.e. hypertelorism, coloboma), and defects of the distal limbs, heart, esophagus, and kidney [121–123]. One prospective study observed an increased risk for major birth defects of 26% after first-trimester exposure to mycophenolate [123]. A transplantation pregnancy registry reported a major birth defect rate of 23% [124].

Breastfeeding

NSAIDs are excreted in low amounts into breast milk. Ibuprofen is the drug of first choice, because of the short half-life and the minimal transfer to breast milk [125].

Prednisone and prednisolone are the corticoids of choice for systemic use in breastfeeding mothers. Published data indicate that a maternal dose of up to 20 mg/day results in low milk levels (RID <2%) [126, 127]. At higher doses (80 mg/day), the infant would ingest less than 10% of the endogenous cortisol production [126]. No adverse events have been observed in breastfed infants.

Even though in 2001 some authors have advised against cyclosporine use during breastfeeding [128], more recent data indicate that this drug is compatible with breastfeeding if the child can be adequately monitored (table 5). Cyclosporine is excreted into breast milk in variable amounts, but data on approximately 20 mother-child pairs have shown that RID is about 2% [129]. In most infants, cyclosporine plasma concentrations were below the detection limit. However, isolated case reports showed detectable blood levels, despite relatively low milk concentrations [130, 131]. No clinical adverse effects have been reported in breastfed infants. Tacrolimus treatment is compatible with breastfeeding under clinical monitoring of the infant. Tacrolimus excretion into breast milk is low (RID ≤0.5%) [132, 133]. Infant plasma concentrations are usually undetectable, and no adverse effects in breastfed infants have been reported. Since there is no information available on mycophenolate use during breastfeeding, this drug should be avoided.

Vaccines

Pregnancy

There is no evidence that live or inactivated vaccines have embryo- or fetotoxic effects (table 6). Live vaccines have a theoretical risk of fetal infection and should therefore be avoided during pregnancy (i.e. measles, mumps, rubella, varicella, yellow fever) [9]. Routine vaccination should be updated before pregnancy and vaccination during pregnancy may be performed in case of obvious risk of infection to protect mother and child [9]. Maternal immunization is increasingly considered as a way to protect young infants against infection. As an example, the Center for Disease Control and Prevention (CDC) recommends routine influenza vaccination even during the first trimester [134]. CDC also recommends that women receive the pertussis vaccine during the third trimester of each pregnancy to provide early life protection to the newborn [135].

Table 6. Vaccines in pregnant and lactating CF patients

Drug	Pregnancy			Lactation		
	safety data	compatibility	recommendations	level of exposure	compatibility	recommendations
Inactivated vaccines	Numerous human data	Drug of choice in pregnant CF patients	Before pregnancy, update routine adult vaccines. During flu season, pregnant women should be immunized against influenza, even during the first trimester	n.a.	Drug of choice in lactating CF patients	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	n.a.	Drug of choice in lactating CF patients	Breastfeeding women may be immunized with live attenuated vaccines using standard recommended doses for adults

n.a. = Not applicable.

Breastfeeding

Breastfeeding women can be immunized with live or inactivated vaccines using standard recommended doses for adults (table 6). All vaccines are considered safe during breastfeeding, with the exception of smallpox vaccine that should not be administered to nursing women and yellow fever vaccine that should only be administered to nursing mothers travelling to high-risk yellow fever-endemic areas [136].

Conclusion

As most of the drugs representing CF treatment lines cross the placenta or are excreted into human milk, they can potentially affect the fetal development or the breastfed infant. Research addressing the risks and benefits of drugs used in CF patients during pregnancy and lactation is often incomplete or challenged by limited methodology, which often leads to conflicting or inconclusive results (e.g. results uncontrolled for some important confounding factors, limited sample size). Nevertheless, except for mycophenolate and misoprostol, none of the drugs in CF therapeutic arsenal are known to be major teratogens. Several drugs have limited systemic absorption and, therefore, even if the available safety data are scarce, no adverse effects are expected in utero or via breast milk (e.g. inhaled use of colistin, topical or oral nystatin, digestive enzymes, most laxatives). However, some drugs should be used with caution because of small teratogenic or fetotoxic risks (e.g. tetracyclines after 15th week of gestation, sulfonamides during the first trimester and near to delivery, NSAIDs during the second and third trimesters). Others should not

be considered as drugs of first choice in pregnant or lactating CF patients as they are associated with theoretical risks (e.g. systemic use of aminoglycosides; quinolones; live attenuated vaccines) or data are currently inconclusive (e.g. fluconazole, systemic glucocorticoids, vitamin A >10,000 UI). Finally, limited available safety data in humans render the risk assessment difficult for some drugs (e.g. intravenous colistin, intravenous amphotericin B, CFTR modulators, ursodeoxycholic acid, bisphosphonates). Yet, potential treatment benefits for CF patients most often outbalance consequences of maternal health deterioration and potential risks for the unborn child.

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