Safety of Medications During Pregnancy and Breastfeeding: Infants of Drug-Addicted Mothers

43

Karel Allegaert, Tim van Mieghem, and John N. van den Anker

Contents

K. Allegaert (✉)
Neonatal Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium

Department of Development and Regeneration, KU Leuven, Leuven, Belgium

Intensive Care and Department of Pediatric Surgery, Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands
e-mail: karel.allegaert@uzleuven.be

T. van Mieghem
Department of Development and Regeneration, KU Leuven, Leuven, Belgium

Obstetrics and Gynecology, University Hospitals Leuven, Leuven, Belgium
e-mail: tim.vanmieghem@uzleuven.be

J. N. van den Anker
Division of Pediatric Clinical Pharmacology, Children's National Health System, Washington, DC, USA

Departments of Pediatrics, Integrative Systems Biology, Pharmacology and Physiology, George Washington University, School of Medicine and Health Sciences, Washington, DC, USA

Intensive Care and Department of Pediatric Surgery, Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands
e-mail: jvandena@childrensnational.org

G. Buonocore et al. (eds.), *Neonatology*,
https://doi.org/10.1007/978-3-319-29489-6_192

Abstract

Any decision on maternal pharmacotherapy should be balanced, comparing maternal and fetal/neonatal outcome to withholding any treatment. This is because there is a relevant body of evidence that uncontrolled maternal conditions also affect fetal outcome. The same holds true for breastfeeding.

Drugs are not thoroughly evaluated for use during pregnancy or breastfeeding. Knowledge on safety of drugs exposure during fetal and neonatal (breastfeeding) life is limited. Pregnancy category classifications for drugs are currently used, but have their limitations. Pregnancy exposure registries to build knowledge have been implemented in the recently revised version of the FDA labelling guidelines (Pregnancy and Lactation Labeling Final Rule).

Suggestive indicators of "likely safe during breastfeeding" are (i) drugs commonly administered to infants, (ii) drugs that are not absorbed following oral administration, (iii) not excreted into human milk, and finally (iv) drug considered safe during pregnancy, since fetal exposure is generally longer and more extensive. Aspects of opioids, benzodiazepines, and anti-epileptics use during fetal life or via breastfeeding have been discussed to illustrate the concepts of pregnancy-related clinical pharmacology, followed by a focused discussion on neonatal abstinence syndromes. We hereby aim to provide the practicing clinician with some guidance and sources of information.

43.1 Salient Points

- Drugs administered to the mother may have harmful effects on the fetus at any time during pregnancy. Decisions on maternal pharmacotherapy should always take account of the effects of withholding maternal treatment on maternal, fetal, and neonatal outcomes.
- The placenta should not be considered as a perfect, absolute barrier and neither is the fetus an inactive bystander following maternal and consequent fetal drug exposure.
- The same rationale holds true for breastfeeding. The goal of maternal medications during breastfeeding should fulfill two criteria: (1) provide safe and effective pharmacotherapy for maternal condition(s) and (2) assure safety or tolerance of the nursing infant from adverse events related to the maternal pharmacotherapy.
- A common misconception about drug safety is "when in doubt, do not provide breastfeeding," since breastfeeding itself provides benefits to both infant and mother.
- Suggestive indicators of "likely safe during breastfeeding" are (i) a drug commonly administered to infants (e.g., antibiotics), (ii) a drug that is not absorbed following oral administration (e.g., aminoglycosides, propofol), (iii) a drug that is not excreted into human milk (e.g., insulin, heparin), and (iv) a drug considered safe during pregnancy since fetal exposure is generally longer and more extensive.
- Breastfeeding rarely needs to be discouraged, discontinued, or interrupted when the mother needs drug therapy, but some caution should be taken with analgosedatives (opioids, benzodiazepines). Radioactive-labeled diagnostic drugs such as lithium, iodine, gold, and ergotamine alkaloids are high-risk drugs and are likely not to be compatible with breastfeeding.
- The Pregnancy and Lactation Labeling Final Rule should provide the tool to generate and collect reliable information on maternal drug use during breastfeeding.

43.2 Introduction

Drug labeling rarely includes information about dosing, efficacy, and maternal, fetal, or newborn safety and commonly states that "the drug has not been studied during pregnancy or breastfeeding." In general, drugs are not thoroughly evaluated for use during pregnancy. This is neither the case for specific pregnancy-related diseases (e.g., gestational diabetes, nausea and vomiting of pregnancy) nor for the impact of pregnancy, delivery, or the postpartum period (e.g., breastfeeding) on pharmacotherapy of nonpregnancy-related

comorbidities (e.g., epilepsy, depression, pain syndromes, posttransplant, asthma, oncological diseases) (Zaijcek and Giacoia 2007; Pavek et al. 2009). A similar case can be built for early infancy and results in extensive off-label and unlicensed pharmacotherapy in both subpopulations (▶ Chap. 44, "Developmental Pharmacology and Therapeutics in Neonatal Medicine") and hence patient anxiety and prescriber liability.

Simple extrapolation from data in adults is hazardous, since pregnancy itself affects pharmacokinetics (PK, concentration-time profile) in part driven by the hormonal (e.g., estradiol) and physiological (e.g., cardiac output, renal function, plasma volume, and protein-binding capacity) changes. This results in extensive variability in drug response. In general, renal elimination capacity is increased throughout pregnancy (i.e., higher glomerular filtration rate, higher active tubular transport). Similarly, basal metabolic activity is also increased. This commonly results in higher drug metabolism (phase I and phase II processes), although these changes are in part also isoenzyme specific. This – although rare – may even result in reduced enzymatic activity during pregnancy (Ramoz and Patel-Shori 2014; Thomas and Yates 2012). Finally, changes in body weight or protein-binding capacity can affect the volume of distribution. Protein-binding capacity and the subsequent free fraction may also have an impact on the amount of drug that will be transferred from the maternal plasma to the human milk compartment (Ramoz and Patel-Shori 2014; Thomas and Yates 2012; Feghali and Mattison 2011). Despite the limited available knowledge, women during pregnancy as well as in the postpartum period need pharmacotherapy for different medical relevant conditions, either or not pregnancy related (Thomas and Yates 2012).

Drugs may have harmful effects on the fetus at any time during pregnancy. However, any decision on pharmacotherapy should always be balanced, comparing maternal and fetal/neonatal outcome to withholding maternal treatment. This is because there is also a relevant body of evidence that uncontrolled or suboptimal controlled maternal conditions in themselves also affect fetal well-being and perinatal outcome. A linear, too simplistic approach to discontinue drugs due to a perceived, association related risk, while ignoring the risks of discontinuation, is unwarranted and often dangerous (e.g., epilepsy, depression, pain syndromes, posttransplant, asthma, or oncological diseases) (Briggs et al. 2015; Gadot and Koren 2015; Amant et al. 2015).

The same rationale holds true for breastfeeding. Human milk is the obvious golden reference and the normative standard feeding for newborns and infants, but may result in breastfeeding associated drug exposure. As extensively discussed in another chapter of this textbook, drug disposition [***a***bsorption, ***d***istribution, and subsequent elimination, either through ***m***etabolic elimination or through primary renal ***e***limination (ADME) pharmacokinetics] in early infancy also differs substantially between children and adults. In general, neonates have an overall low clearance capacity with an importance between the subject explained by covariates such as organ weight and function, body composition, size, co-administration of drugs, genetic polymorphisms, growth restriction, or disease characteristics.

As a consequence, the ultimate goal of maternal medications during breastfeeding should fulfill two criteria: (1) provide safe and effective pharmacotherapy for the maternal condition(s) and (2) still assure safety or tolerance of the nursing infant from adverse events related to the maternal pharmacotherapy (Sachs and Committee on Drugs 2013). As a geneal comment before we discuss more in detail some aspects of maternal–fetal pharmacotherapy, pharmacotherapy during breastfeeding, and the neonatal abstinence syndromes, we would like to make the point that compound or class-specific information on drug use during pregnancy, postpartum, and breastfeeding is evolving and has become a field of active clinical research.

This means that updated, reliable information should be easy accessible for caregivers. Besides textbooks, LactMed is a free online database with information on drugs and lactation as one of the newest additions to the National Library of Medicine's TOXNET system. The Motherisk program has also an updated and useful website

(www.motherisk.org) that can be searched and is open for advices. Another source of information with specific emphasis on teratology is the www.mothertobaby.org website. More recently (cf. infra), pregnancy exposure registries have been introduced in the FDA labeling concept, aiming to improve the available knowledge and access to knowledge on drugs and pregnancy. Also the National Center on Birth Defects and Developmental disabilities, integrated in the Centers for Disease Control (CDC), provides information on the safety of maternal drug use (www.cdc.gov/pregnancy/meds/treatingfortwo). Supported by the National Health Services (NHS) (www.rdtc.nhs.uk/services/teratology), the UK Teratology Information Service (UKTIS) website provides information, including monographs. Through the same group, the Best Use of Medicines in Pregnancy (BUMPS, www.medicinesinpregnancy.org) aims to inform and be informed by the public.

43.3 Maternal–Fetal Pharmacotherapy

Maternal pharmacotherapy may sometimes have a primary fetal indication, with maternal administration of steroids for fetal lung maturation as the best known maternal exposure, aimed for improved fetal and neonatal outcome. Transmaternal fetal therapy clearly reflects the fact that the placenta should not be considered to be a *perfect, absolute barrier* and neither is the fetus an *inactive bystander* following maternal and subsequent fetal drug exposure (Rowe et al. 2013). Consequently, effects (e.g., lung maturation, conversion of supraventricular tachycardia) but also harmful drug-related fetal side effects may occur at any time throughout pregnancy.

Structural, teratogenic effects, i.e., prenatal toxicity characterized by structural defects (e.g., mono-organ like cardiac, central nervous system, or renal, but sometimes also multi-organ) in the developing embryo or fetus, are the most commonly seen between (already) the 3rd and 11th week of pregnancy (Thomas and Yates 2012). This is of relevance when a physician considers a prescription in any female patient of childbearing age (e.g., angiotensin-converting enzyme inhibitors, coumarins, antiepileptics, isotretinoin). In contrast, drug exposure during the second and third trimester of pregnancy more generally affects either fetal growth or functional development (e.g., illicit drugs). Finally, perinatal exposure (e.g., opioids, benzodiazepines, antidepressants) may affect neonatal adaptation.

Studying the safety and the efficacy of drugs in pregnancy is obviously more limited, since it is ethically inacceptable to subject pregnant women to drugs for the sake of studying fetal and maternal safety (Briggs et al. 2015). However, capturing observations on human exposure in a structured approach may also provide relevant information despite the fact that such information may be confounded by maternal disease state. Case–control studies, observational studies and the use of prospective registration during pregnancy may provide more robust information. Such methods facilitate comparison of exposure rates to a specific compound in mothers who deliver a newborn with a specific malformation versus those who delivered a healthy baby (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.html).

Largely because of these limitations, the assessment of risks and how to handle the available evidence, association, or likelihood of fetal harm related to maternal pharmacotherapy remains a difficult, balanced decision. This is also reflected by the different and evolving applied approaches: *strategies evolve, but also vary.*

Pregnancy category classifications are one approach, but classifications vary somewhat between different authorities, and these categories do not include risks related to drugs or their metabolites transferred through breast milk. The concept of pregnancy exposure registries to build knowledge has been integrated in the recently revised version of the Food and Drug Administration (FDA) labeling guidelines on medication guidelines during pregnancy and lactation. FDA defines a pregnancy exposure registry as a study that collects information from women who take prescription medicines or vaccines during

pregnancy. This information includes data on the newborn and is compared with women not taken drugs during pregnancy (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.html).

The FDA medication classification system initially applied a category A, B, C, D, X, and N for each compound and required a quite large amount of high-quality data to be defined as pregnancy category A (i.e., safe to the fetus). In the meanwhile, the FDA requests a more narrative description of the evidence available for use of the drug in pregnancy in three subsections, "pregnancy," "lactation," and "females and males of reproductive potentials." The "pregnancy" subsection provides information to the use of the drug in pregnant women, including dosing and potential fetal risks, and will be based on the earlier-mentioned registries. The "lactation" section will provide information about the use of the drug while breastfeeding, such as the amount of drug in human milk and potential effects on the nursing infant. This new Pregnancy and Lactation Labeling Final Rule became effective by June 30, 2015 (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.html).

43.4 Breastfeeding

Lactating women are regular users of medications and are often advised to either discontinue or even stop nursing while taking drugs, despite the fact that there are only a limited number of drugs that have been identified as potentially harmful to the newborn.

A common misconception about drug safety is "when in doubt, do not provide breastfeeding," since breastfeeding itself provides relevant benefits to both the infant and the mother (Genung 2013). The earlier-described Pregnancy and Lactation Labeling Final Rule should provide the tool to generate and collect more reliable information on this topic. At present, there are still a limited number of prospective population-based studies or systematic reviews that provide some insight in the extent and the relevance of the problem (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.html). Already two decades ago, Ito et al. quantified the incidence of adverse reactions (11.2%) in a cohort of 838 nursing infants with mothers on drugs (Ito et al. 1993). More importantly, all events were classified as minor and were most commonly associated with antibiotics, analgesics/narcotics, antihistamines, sedatives, antidepressants, or antiepileptics. In 2003, this overall pattern was confirmed by Anderson et al., following a systematic review of 100 published case reports. None of the cases were "definite," 47% "probable," and 53% "possible" related to breastfeeding. Central nervous system-related drugs accounted for about 50% of the events and also included three fatalities. These observations suggest that when a few simple precautions are taken in drug selection and when the infant's age is taken into account, breastfeeding rarely needs to be discontinued when the mother needs pharmacotherapy: adverse drug reactions in breastfed infants are *less than imagined* (Anderson et al. 2003).

Maternal absorption of a given dose of drug (D_m) will result in compound-specific, variable transfer of the drug into the human milk (D_i). However, concentrations in human milk usually are quite low, and the oral bioavailability following oral ingestion by the infant is also a very relevant and often forgotten covariate to estimate the subsequent exposure (RID = relative infant dose, D_m/D_i * absorption) (Fig. 1). In Fig. 1, the differences in drug concentrations in the infant (1 vs. 2) can be explained by the presence (*a*) or absence (*b*) of "*an initial concentration following fetal exposure to the drug*" since accumulation in the infant relates to dose and duration, body composition, the clearance capacity of the infant, but also the initial concentration in the newborn's compartments.

In the clinical setting, suggestive indicators of "likely safe during breastfeeding" are (*i*) a drug commonly administered to infants (e.g., antibiotics), (*ii*) a drug that is not absorbed following oral administration (e.g., aminoglycosides, propofol), (*iii*) not excreted into human milk (e.g., insulin, heparin), and finally (*iv*) a drug considered safe

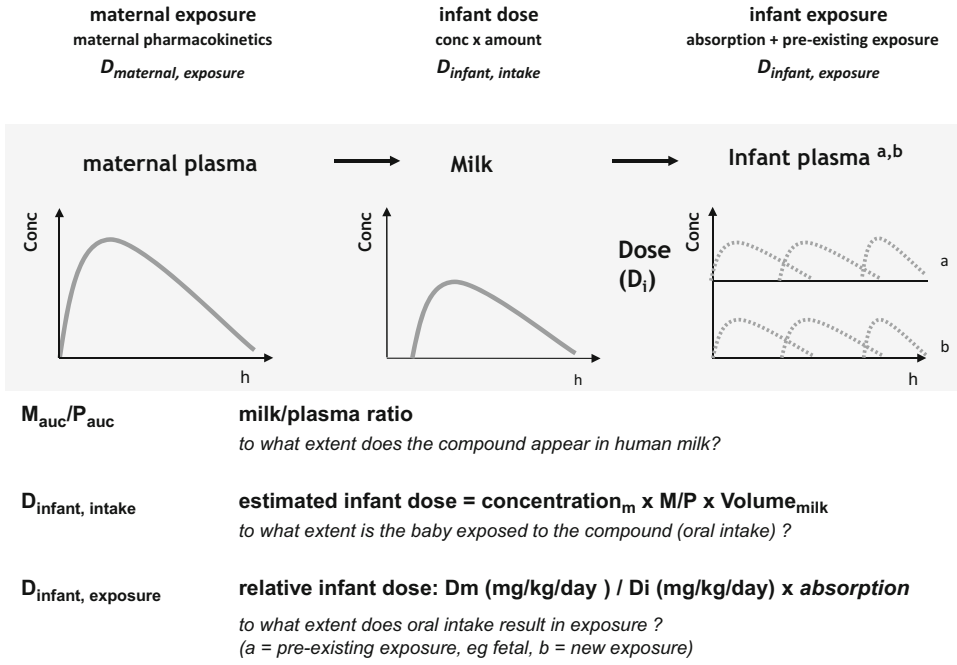

Fig. 1 Pharmacokinetics of mother–infant pairs as it relates to drug exposure through breastfeeding. Maternal absorption of a given dose of drug (D_m) will result in compound-specific, variable transfer of the drug into the human milk (D_i). However, concentrations in human milk usually are quite low, and the oral bioavailability following oral ingestion by the infant is also a very relevant and often forgotten covariate to estimate the subsequent exposure (RID = relative infant dose, D_m/D_i * absorption). The differences in drug concentrations in the infant (1 vs. 2) can be explained by the presence (*a*) or absence (*b*) of *an initial concentration following fetal exposure to the drug* since accumulation in the infant relates to dose and duration, body composition, the clearance capacity of the infant, but also the initial concentration in the newborn's compartments

during pregnancy, since fetal exposure is generally longer and more extensive. In contrast, e.g., radioactive-labeled diagnostics, lithium, iodine, gold, and ergotamine alkaloids are high-risk drugs, more likely not compatible with breastfeeding. The available data suggest that breastfeeding rarely needs to be discouraged, discontinued, or interrupted when the mother needs drug therapy, but some caution may be warranted with analgosedatives (opioids, benzodiazepines) (Van den Anker 2012; Berlin and van den Anker 2013; Hendrickson and McKeown 2012). In contrast, local anesthetics, systemic non-opioid analgesics, and intravenous or inhalational anesthetics are safe in the setting of breastfeeding (Allegaert and van den Anker 2015).

Peripartum opioid exposure became a specific focus of interest, following a case report of morphine intoxication in a breastfed neonate of a codeine-prescribed mother (Koren et al. 2006). Subsequent guidelines (lowest codeine dose possible, maternal exposure <4 days, and switch to non-opioids as soon as possible, monitor maternal and neonatal sedation) resulted in an eightfold reduction (5/238, 2.1%) in the incidence of neonatal sedation and were only associated with prolonged (>4 days) maternal codeine intake. As part of analgosedative treatment options, mothers after delivery (e.g., post-caesarean, birth-related injuries, but also preexisting pain syndromes) can be exposed to different analgosedatives that may also have impact of the breastfed infant (Van den Anker 2012; Allegaert and van den Anker 2015). This will be followed by some guidance on the use of antiepileptic drugs and breastfeeding. Aspects related to antidepressants will be covered in the section on neonatal

abstinence syndrome. We hereby also cover some aspects of fetal exposure, since for some drugs, e.g., antiepileptic drugs, neonates are exposed both intrauterine and during breastfeeding.

43.4.1 Opioids

The breastfeeding rate increased steadily in the developed world (Saadeh 2012). More recently, opioid consumption in the general population – including women of childbearing age – also raised steadily (DeVane 2015). This means that the clinical experience with maternal opioids is still relatively limited with emerging data on (side) effects with codeine, oxycodone, methadone, and tramadol during breastfeeding (Rowe et al. 2013; Berlin and van den Anker 2013; Koren et al. 2006). The same phenomenon also explains the dramatic increase in the incidence of neonatal abstinence syndrome (cf infra). Referring to Fig. 1, oral absorption of opioids in neonates should be anticipated, while the extent of exposure through mother's milk will depend on maternal ingestion (dose) and metabolism. Neonatal drug elimination relates to the neonate's metabolic or renal elimination, but will be relatively limited (Allegaert et al. 2013). These circumstances have the potential to result in side effects in individual infants. A pivotal case report in 2006 of Koren et al. on codeine-related poisoning in an infant due to breastfeeding following maternal intake of codeine reinitiated the clinical interest and research on maternal–infant opioid pharmacokinetics and dynamics and its covariates (Koren et al. 2006). A pharmacogenetic link with maternal ultrafast metabolizer status for cytochrome p450 (CYP) 2D6 was documented. This genetic status results in higher and faster conversion of codeine to morphine (Koren et al. 2006). More recently, the same researchers also described that a combination of maternal genetic polymorphisms (i.c. CYP 2D6 and P-glycoprotein polymorphisms) predicted 87% of the maternal and infant central nervous system depression cases with a sensitivity of 80% and a specificity of 87% in a cohort of 111 breastfeeding mother–infant dyads (Sistonen et al. 2012). Unfortunately, this observation is not limited to codeine only.

The incidence of central nervous system depression in breastfed neonates following maternal exposure to oxycodone, codeine, or paracetamol was retrospectively compared in 533 mother–infant pairs. Lam et al. hereby clearly showed that there was a 20.1% rate of depression in infants of nursing mothers on oxycodone, as compared with 16.7% and 0.5% when treated with codeine or paracetamol, respectively (Lam et al. 2012). Finally, using a sparse sampling study design to assess transfer of tramadol and *O*-desmethyl tramadol into transitional breast milk, the relative infant dose of 2–3% remained very limited. Based on these observations, the authors concluded that short-term maternal use of tramadol is compatible with breastfeeding (Salman et al. 2011).

It remains somewhat difficult to convert the available observations in the literature to clinical guidelines for pediatricians, but we tried to provide some guidance (Van den Anker 2012; Allegaert and van den Anker 2015; DeVane 2015). Firstly – besides tramadol – it seems reasonable to anticipate that sedation may occur following maternal exposure to codeine, oxycodone, methadone, or morphine. Secondly, and clinical quite useful, there is a high concordance between maternal and neonatal somnolence. When the mother exhibits somnolence, the baby should be examined. This is likely due to the impact of genetic polymorphisms and dose on the individual maternal–infant-related effects and side effects of these drugs. Severe somnolence only emerges after 4 days of continued drug exposure and subsequent drug accumulation. When the human milk volume increases, exposure (mg/l x volume) increases and is prolonged, making subsequent accumulation in the infant more likely. As a result of the above premises, maternal opioid exposure for more than 72 h after delivery warrants specific clinical evaluation, with emphasis on signs of sedation in both the mother and the newborn (Van den Anker 2012; Salman et al. 2011; Rivers et al. 2012).

There are two additional comments to be made. Firstly (Fig. 1), this rationale does not fully apply to newborns already exposed prenatally to opioids, but these aspects will be discussed in the

section on neonatal abstinence syndrome. Secondly, the route of administration of opioids obviously matters (systemic, e.g., oral, intravenous, or transcutaneous, or locoregional, e.g., spinal, epidural). Because of the much lower doses used and the lower plasma concentrations, the subsequent drug exposure through human milk will be much lower.

43.4.2 Benzodiazepines

Benzodiazepines (e.g., diazepam, lorazepam, midazolam) are commonly administered as anxiolytics. These compounds and some of their metabolites can be retrieved in human milk, but the amounts remain very low and subsequent exposure remains very limited (Cole and Hailey 1975; Nitsun et al. 2006). In 24 h of human milk collection after a single dose, only 0.005% of the maternal midazolam dose was retrieved. Taking the subsequent oral bioavailability (50–60%) into account, it is very reasonable to assume that the exposure will be very low when administered after delivery. In contrast, plasma diazepam and its active metabolite (desmethyldiazepam) could be measured up to 7–10 days of postnatal age in neonatal plasma samples after administration to the mother before or during delivery (Cole and Hailey 1975). We once again refer to Fig. 1 to explain this. Following administration during delivery, the fetus and newborn will have already a relevant concentration of benzodiazepines in the blood (Fig. 1, *level a instead of level b*), and the neonatal clearance capacity for these compounds is limited (De Wildt et al. 2002).

43.4.3 Antiepileptic Drugs

Continuation of antiepileptic treatment during pregnancy and the postpartum period is extremely important, since poor epileptic control has been associated with adverse maternal and fetal outcomes. Monitoring of maternal drug levels is often advised since pharmacokinetics may change. However, the safety of breastfeeding while taking antiepileptic drugs (AEDs) remains of some concern. This concern is also reflected in the fact that the rates of breastfeeding of women on AEDs are lower when compared to women not on AEDs living in the same region or country (Veiby et al. 2015). Moreover, women using either AED poly-therapy (75%) or lamotrigine (undergoes glucuronidation, so poorer clearance capacity in early neonatal life) had even lower breastfeeding initiation rates (70%), when compared to either the reference group (not on AEDs, 92%) or to women on AED monotherapy (80%), with a subsequent similar decline in breastfeeding rates with time (at 3 months, AED poly 67%, lamotrigine 60%, reference group 86%, AED mono 70%). Obviously, many factors affect the decision to initiate and maintain breastfeeding. Besides socioeconomic and social factors, emotional status or self-esteem but also disease-related aspects (e.g., need for day/night routine, seizure control) likely affect the individual decision of women (Veiby et al. 2015; Meador et al. 2014).

43.4.3.1 Compound-Specific Risk Assessment

Phenytoin, carbamazepine, and valproate are generally considered to be safe AEDs during breastfeeding (Veiby et al. 2015). Phenytoin and valproate have a high and carbamazepine a moderate high plasma protein binding. Consequently, the M/P ratios are quite low (phenytoin, 0.1–0.6; carbamazepine, 0.2–0.7; valproate, 0.01–0.3). Some suggest checking liver enzymes and thrombocytes in the nursing infant exposed to valproate and liver enzymes in infants exposed to carbamazepine (Veiby et al. 2015).

Lamotrigine, oxcarbazepine, levetiracetam, topiramate, gabapentin, pregabalin, vigabatrin, and tiagabine are classified as moderately safe AEDs. As mentioned earlier, lamotrigine (M/P ratio 0.4–0.67) is cleared by glucuronidation and is moderately plasma protein bound (55%). We suggest monitoring the infant for clinical signs and consider checking serum levels when the infant displays poor suckling. We hereby have to take into account that the free lamotrigine

fraction in neonatal serum will be higher when compared to maternal plasma (lower binding capacity) (Veiby et al. 2015). Oxcarbazepine (M/P ratio 0.5) has the same route of metabolic elimination (glucuronidation), but clinical experience with this compound is much more limited. The M/P ratio of levetiracetam is much higher (M/P ratio 0.8–1.6), but clearance is through primary renal elimination, and there is a relevant amount of clinical experience with this compound to treat neonatal seizures (Pressler and Mangum 2013). For all the other compounds mentioned, there are only a limited number of clinical reports.

Finally, benzodiazepines, phenobarbital and primidone, ethosuximide, zonisamide, or felbamate, are classified as potential hazardous. Aspects on benzodiazepines have been discussed earlier (3.2). For phenobarbital and its prodrug primidone, accumulation may occur because of the very long elimination half-life of phenobarbital in neonates (Marsot et al. 2014). Again, clinical observation and – in the presence of symptoms – drug monitoring seem a very reasonable choice. Ethosuximide has a high M/P ratio, and the relative infant dose (32–113%) and subsequent levels in neonates are quite high (24–75%) when compared to maternal levels. Since ethosuximide is commonly part of poly-AED therapy, careful monitoring is recommended. Zonisamide also results in significant exposure (M/P ratio 0.8) and has a long elimination half-life in neonates. There are no data on felbamate, but this drug may induce hepatic failure or aplastic anemia (Veiby et al. 2015).

43.4.3.2 Impact of Prenatal and Breastfeeding-Mediated Exposure of Antiepileptic Drugs (AED) on Neurodevelopmental Outcome

Similar to the breastfeeding rates, the assessment of neurodevelopmental impact of AED exposure through breastfeeding is also hampered by several covariates (Meador et al. 2014). Firstly, postnatal exposure generally follows intrauterine exposure. Secondly, the impact of fetal exposure to AEDs during pregnancy also affects subsequent neurodevelopmental outcome (e.g., gross motor skills, fine motor skills, social skills). These neurodevelopmental observations further add to the available data on the impact of fetal exposure on the incidence of congenital malformations (Meador et al. 2014). AEDs such as valproate (9.3%, RR 5.1 to lamotrigine) and phenobarbital (4.2%, RR 2.9) are associated with a higher risk of major malformations than newer AEDs such as lamotrigine (2%) and levetiracetam, (2.4%), while topiramate (3%, RR 2.2) was associated with an increased risk of cleft lip compared with that of a reference population (Veiby et al. 2013).

As reported by the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) group, fetal valproate exposure is associated with a significantly higher risk of impaired cognitive function at 3 years (mean IQ 92, mean IQ difference of 6–9 when compared to carbamazepine, lamotrigine, or phenytoin, 258 cases of AED exposure) with a clear dose–effect relation for valproate (Meador et al. 2009). Similarly, Veiby et al. (Marsot et al. 2014) confirmed the impact of fetal AED exposure on psychomotor development. At age 6 years, infants of mothers using antiepileptic drugs ($n = 223$) had a higher risk of impaired fine motor skills compared with the reference group (11.5–4.8%, OR 2.1). The maternal treatment with multiple antiepileptic drugs was associated with adverse outcome for fine motor skills (25.0–4.8%, OR 4.3) and social skills (22.5–10.2%, OR 2.6).

Building on these background characteristics, the same study also documented that breastfeeding in infants of women using AEDs was associated with improved neurodevelopment outcome at ages 6 and 18 months, compared with those with either no breastfeeding or breastfeeding for less than 6 months (Meador et al. 2014). At 36 months, fetal AED exposure was associated with adverse development, regardless of breastfeeding. Children of women with epilepsy but without AED during pregnancy had normal development at 6 months. Based on these observations, it is fair to encourage women with epilepsy to breastfeed their infants, irrespective of antiepileptic drug treatment and taking the

abovementioned suggestions on clinical monitoring into account (Meador et al. 2014).

43.5 Neonatal Withdrawal Syndromes

Neonatal withdrawal or neonatal abstinence syndrome (NAS) is a withdrawal syndrome in neonates due to acute cessation of the exposure to either illicit or prescribed drugs. Similar to tolerance or dependence, withdrawal may occur as a result of repeated or chronic administration of drugs, but also after short-term high-dose use, e.g., during neonatal stay. Consequently, NAS can appear both following discontinuation of drugs taken by the pregnant mother and following discontinuation of drugs administered intentionally to the newborn. The most commonly involved compounds are opioids, selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, as well as cannabis or nicotine.

43.5.1 Opioid-Related Neonatal Abstinence Syndrome

The incidence of opioid-related neonatal abstinence syndrome (NAS) has increased significantly in the last decade, colinear with the increased medical use of prescription opioids in adults (DeVane 2015). The impact on the trends of NAS incidence throughout the Western world has been illustrated in Fig. 2 (Turner et al. 2015; Dow et al. 2012; Patrick et al. 2012, 2015; O'Donnell et al. 2009; Creanga et al. 2012). This means that NAS is no longer "restricted" to illicit drug users but also has become a frequent complication following medical prescription of opioids (DeVane 2015). The clinical picture of neonatal abstinence syndrome mimics to a large extent the syndrome of opioid withdrawal in adults ("cold turkey") and includes both neurological (e.g., agitation, crying, sleep disturbance, feeding difficulties, but also seizures) and extra-neurological symptoms (e.g., diarrhea, vomiting, perianal excoriations, sneezing, sweating, hyperthermia). The

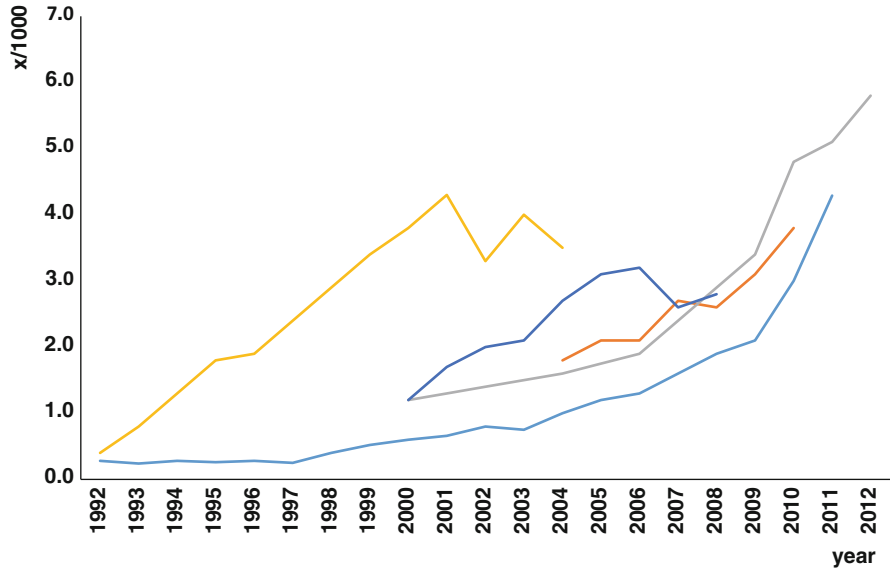

Fig. 2 The impact on the trends of NAS incidence throughout the Western world is illustrated by the trends in the annual incidence (1/1000) of neonatal abstinence syndrome in different cohorts as published between 1992 and 2012 (Turner et al. 2015; Dow et al. 2012; Patrick et al. 2012, 2015; O'Donnell et al. 2009; Creanga et al. 2012)

clinical presentation of NAS varies with the opioid (elimination half-life short or prolonged, heroin vs. methadone) used, co-drugs, maternal drug history, placental transfer, neonatal elimination capacity, but also pharmacogenetics (e.g., drug metabolism, transporters, receptor polymorphisms) (Wachman et al. 2013).

Table 1 Items and calculation of the modified Finnegan score (DeVane 2015; Hudak et al. 2012)

Central nervous system symptom-related items		
High-pitched cry	Present	2
	>2 h	3
Sleeps less than	3 h after feeding	1
	2 h after feeding	2
	1 h after feeding	3
When disturbed	Mild tremors	1
	Marked tremors	2
When undisturbed	Mild tremors	3
	Marked tremors	4
Increased muscle tone		2
Excoriation of the skin		1
Myoclonic jerks during sleep		3
Generalized convulsions		5
Autonomous/vegetative symptom-related items		
Sweating/ perspiring		1
Body temperature	37.5–38 °C	1
	>38 °C	2
Frequent yawning		1
Mottling		1
Nasal stuffiness		2
Sneezing		1
Gastrointestinal and respiratory system symptom-related items		
Frantic suckling		1
Poor feeding		2
Regurgitation		2
Projectile vomiting		3
Stools	Loose	2
	Watery	3
Tachypnea	>60/min	1
	>60/min + retractions	2

The Finnegan score (modified version, 21 items, 0–37 points, Table 1) is universally used to quantify the severity of withdrawal symptoms (Hudak et al. 2012). The score hereby reflects the central nervous system driven as well as autonomic, intestinal, and respiratory signs (Zimmermann-Baer et al. 2010). To document a threshold for suspected NAS, Zimmermann-Baer et al. documented the Finnegan score in 102 neonates (>34 weeks gestational age), up to the age of 5–6 weeks. The 95th percentile increased from 5.5 on day 1 to 7 on day 2, and at 5–6 weeks, the 95th percentile was 8 during daytime and 6 at nighttime (Zimmermann-Baer et al. 2010). Based on these observations, the authors suggest that values above 8 should raise suspicion of withdrawal. When pharmacological treatment of opiate withdrawal in neonates is deemed necessary, opiates (morphine, methadone, preferably by oral route) are the first choice, with subsequent slow weaning, although there is extensive variability in weaning and discharge practices (Hudak et al. 2012). In the event of non-opioid neonatal withdrawal, phenobarbital is the first choice. More recently, clonidine (5 μg/kg per day, divided in 8 doses) has been suggested as a novel treatment modality (Bada et al. 2015). Similarly, buprenorphine by sublingual route may also become a new treatment modality (Ng et al. 2015).

Besides pharmacological interventions, we strongly recommend to consider the impact of other interventions like swaddling, traditional supportive interventions, but also breastfeeding (MacMullen et al. 2014). Although there are no prospective randomized controlled trials, there is evidence in support of breastfeeding in women who have used methadone in pregnancy (grade C), since this reduces the incidence (NNT 5–6) and severity of NAS (grade C), without inducing clinically important sedation (grade C) (Lefevere and Allegaert 2015). Optimal NAS treatment remains undetermined and practices vary between and within hospitals. Prolonged length of stay for NAS cases may result in patient harm and impaired maternal–infant attachment, besides significant costs. The development of an educational program and a standard treatment protocol for NAS has

been the most effective interventions to reduce this length of stay for NAS newborns (Asti et al. 2015). Some key messages on neonatal abstinence syndrome for the practitioner are summarized in Table 2 (DeVane 2015; Turner et al. 2015; Dow et al. 2012; Patrick et al. 2012, 2015; O'Donnell et al. 2009; Creanga et al. 2012; Wachman et al. 2013; Hudak et al. 2012; Zimmermann-Baer et al. 2010; Bada et al. 2015; Ng et al. 2015; MacMullen et al. 2014; Lefevere and Allegaert 2015; Asti et al. 2015; Siu and Robinson 2014).

Table 2 Key messages on neonatal abstinence syndrome: essentials for the practitioner (DeVane 2015; Turner et al. 2015; Dow et al. 2012; Patrick et al. 2012, 2015; O'Donnell et al. 2009; Creanga et al. 2012; Wachman et al. 2013; Hudak et al. 2012; Zimmermann-Baer et al. 2010; Bada et al. 2015; Ng et al. 2015; MacMullen et al. 2014; Lefevere and Allegaert 2015; Asti et al. 2015; Siu and Robinson 2014)

The incidence of neonatal abstinence syndrome (NAS) varies extensively (fivefold to tenfold) between units, but there is an overall relevant increase in the incidence of NAS
Besides recreational use, this increase in NAS also reflects a significant increase in the medical prescription of opioids
Fetal exposure does not necessary result in neonatal abstinence syndrome. For heroin and methadone, its incidence is about 60–80 %
The timing of appearance of NAS symptoms in part depends on the clearance characteristics of the opioid (heroin <24–48 h versus methadone 48–72 h) involved. The longer the elimination half-life, the later the symptoms appear
Treatment should be protocol driven, based on assessment (Finnegan) and followed by non-pharmacological as well as pharmacological interventions. Treatment should also cover the subsequent tapering of these drugs
Neonatal seizures are the most life-threatening complication of NAS. Furthermore, treatment aims to reduce the distress (Finnegan score, excessive crying), preserve weight gain, and improve oral feeding
Breastfeeding has a proven positive effect on the incidence and the extent of neonatal abstinence syndrome (NNT = 5–6)
Opioid withdrawal should be treated with opioids, but practices on the preferred compound (methadone, morphine) vary
Although these concepts can also be applied to withdrawal syndromes resulting from other drugs (e.g., antidepressants, sedatives), the available evidence and guidance are more limited

43.5.2 Antidepressants/SSRI-Related Withdrawal Syndromes

Selective serotonin reuptake inhibitors (SSRIs, e.g., citalopram, paroxetine, fluvoxamine) or serotonin–norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine, duloxetine) are commonly used during pregnancy and/or breastfeeding, since depression is a highly prevalent disease in the peripartum period. This incidence is estimated to be as high as 1 in 8 women (Verreault et al. 2014). During pregnancy, antidepressants cross the placenta, but a relevant (i.e., robust and frequent) association with congenital malformations is absent and likely limited to the association between lithium and cardiopathy (RR fivefold to tenfold, but overall risk 1–5% instead of 0.5–1%), most specific for Ebstein's anomaly. Fetal exposure may result in a neonatal clinical syndrome similar to a withdrawal syndrome (poor neonatal adaptation, 30%). SSRIs have also been associated with respiratory distress, persistent pulmonary hypertension (PPHN, absolute risk <1%), and hypoglycemia. However, when evaluating the risk/benefit ratio of SSRI administration in pregnancy, the risk associated with treatment discontinuation (e.g., relapse of psychiatric problems, preterm delivery, postpartum depression) appears to outweigh the risks of therapy continuation. Moreover, maternal depression may negatively affect the child's development, emphasizing the importance of prevention by appropriate treatment during pregnancy with the least minimal effective dose (Ornoy and Koren 2014).

Recently, Reefhuis et al. applied a Bayesian analysis to combine different datasets to explore associations between birth defects and specific SSRIs. None of the earlier reported malformations associated with sertraline were confirmed, and nine previously reported associations between maternal SSRI use and birth defects were rejected (Reefhuis et al. 2015). In contrast, paroxetine (anencephaly OR 3.2; atrial septum defect OR 1.8; right ventricular outflow tract obstruction OR 2.4; gastroschisis OR 2.5; omphalocele 3.5) and fluoxetine (right ventricular outflow tract OR 2; craniosynostosis OR 1.9) have been

associated with malformations (Reefhuis et al. 2015). It his hereby important to stress the fact that these are associations, not necessary reflecting causality. Secondly, the OR values observed only result in a very limited increase in the absolute risks.

43.6 Conclusions

In general, drugs are not thoroughly evaluated for use during pregnancy and/or during breastfeeding. Simple extrapolation from data in adults is hazardous, since pregnancy itself affects pharmacokinetics (PK, concentration–time profile) with a subsequent extensive interindividual variability in drug response (PD, concentration–effect profile). Despite the limited available knowledge, women need pharmacotherapy for different medical relevant conditions during pregnancy as well as in the postpartum period, either or not pregnancy related. However, any decision on pharmacotherapy should always be balanced, comparing maternal and fetal/neonatal outcome to the absence of any maternal treatment. This is because there is also a relevant body of evidence showing that uncontrolled or suboptimal controlled maternal conditions in themselves also affect fetal well-being and outcome. The same rationale holds true for breastfeeding. Compound or class-specific information on its use during pregnancy, the postpartum period, and breastfeeding is evolving. This means that updated, reliable information should be easy accessible for caregivers and suggestions on websites have been provided.

Pregnancy category classifications are one approach, but classifications vary somewhat between different authorities, and these categories do not include risks related to drugs or their metabolites via breast milk. The concept of pregnancy exposure registries to build knowledge has been integrated in the recently revised version of the FDA labeling medication guidelines during pregnancy and lactation. In the clinical setting, suggestive indicators of "likely safe during breastfeeding" are (*i*) a drug commonly administered to infants (e.g., antibiotics), (*ii*) a drug that is not absorbed following oral administration (e.g., aminoglycosides, propofol), (*iii*) not excreted into human milk (e.g., insulin, heparin), and finally (*iv*) a drug considered safe during pregnancy, since fetal exposure is generally longer and more extensive. The Pregnancy and Lactation Labeling Final Rule should also provide the tool to generate and collect more reliable information on maternal drug use during breastfeeding. Aspects of opioids, benzodiazepines, and antiepileptics used during fetal or through breastfeeding were discussed first to illustrate the concepts of pregnancy-related clinical pharmacology, followed by a focused discussion on neonatal abstinence syndrome.

43.7 Summary

Any decision on maternal pharmacotherapy should be balanced, comparing maternal and fetal/neonatal outcome to withholding any treatment. This is because there is a relevant body of evidence that uncontrolled maternal conditions also affect fetal outcome. The same holds true for breastfeeding.

Drugs are not thoroughly evaluated for use during pregnancy or breastfeeding. Knowledge on safety of drugs exposure during fetal and neonatal (breastfeeding) life is limited. Pregnancy category classifications for drugs are currently used, but have their limitations. Pregnancy exposure registries to build knowledge have been implemented in the recently revised version of the FDA labeling guidelines (Pregnancy and Lactation Labeling Final Rule).

Suggestive indicators of "likely safe during breastfeeding" are (*i*) drugs commonly administered to infants, (*ii*) drugs that are not absorbed following oral administration, (*iii*) not excreted into human milk, and finally (*iv*) drug considered safe during pregnancy, since fetal exposure is generally longer and more extensive. Aspects of opioids, benzodiazepines, and antiepileptics used during fetal life or via breastfeeding have been discussed to illustrate the concepts of pregnancy-related clinical pharmacology, followed by a focused discussion on neonatal abstinence syndromes. We hereby aim to provide the practicing clinician with some guidance and sources of information.

Acknowledgments Karel Allegaert is supported by the Fund for Scientific Research, Flanders (fundamental clinical investigatorship 1800214 N), and the research activities are further facilitated by the agency for innovation by Science and Technology in Flanders (IWT) through the SAFEPEDRUG project (IWT/SBO 130033). John van den Anker is supported by NIH (K24DA027992, R01HD048689, U54HD071601) and the European Commission (TINN [223614], TINN2 [260908]. NEUROSIS [223060]).

References

Allegaert K, van den Anker JN (2015) Maternal analgosedation and breastfeeding: guidance for the pediatrician. JPNIM 4, e04117

Allegaert K, Langhendries JP, van den Anker JN (2013) Educational paper: do we need neonatal clinical pharmacologists? Eur J Pediatr 172(4):429–435

Amant F, Han SN, Gziri MM et al (2015) Management of cancer in pregnancy. Best Pract Res Clin Obstet Gynaecol 29:741–753

Anderson PO, Pochop SL, Manoquerra AS (2003) Adverse drug reactions in breastfed infants: less than imagined. Clin Pediatr (Phila) 42:325–340

Asti L, Magers JS, Keels E et al (2015) A quality improvement project to reduce length of stay for neonatal abstinence syndrome. Pediatrics 135:e1494–e1500

Bada HS, Sithisam T, Gibson J et al (2015) Morphine versus clonidine for neonatal abstinence syndrome. Pediatrics 135:e383–e391

Berlin CM Jr, van den Anker JN (2013) Safety during breastfeeding: drugs, foods, environmental chemicals, and maternal infections. Semin Fetal Neonatal Med 18:13–18

Briggs GG, Polifka JE, Wisner KL et al (2015) Should pregnant women be included in phase IV clinical drug trials? Am J Obstet Gynecol 213:810–815

Cole AP, Hailey DM (1975) Diazepam and active metabolite in breast milk and their transfer to the neonate. Arch Dis Child 50:741–742

Creanga AA, Sabel JC, Ko JY et al (2012) Maternal drug use and its effect on neonates: a population-based study in Washington State. Obstet Gynecol 119:924–933

De Wildt SN, Kearns GL, Hop WC et al (2002) Pharmacokinetics and metabolism of oral midazolam in preterm infants. Br J Clin Pharmacol 53:390–392

DeVane CL (2015) An epidemic of opioid prescriptions. Pharmacotherapy 35:241–242

Dow K, Ordean A, Murphy-Oikonen J et al (2012) Neonatal abstinence syndrome clinical practice guidelines for Ontario. J Popul Ther Clin Pharmacol 19:e488–e506

Feghali MN, Mattison DR (2011) Clinical therapeutics in pregnancy. J Biomed Biotechnol 2011:783528

Gadot Y, Koren G (2015) The use of antidepressants in pregnancy: focus on maternal risks. J Obstet Gynaecol Can 37:56–63

Genung V (2013) Psychopharmacology column: a review of psychotropic medication lactation risks for infants during breastfeeding. J Child Adolesc Psychiatr Nurs 26:214–219

Hendrickson RG, McKeown NJ (2012) Is maternal opioid use hazardous to breast-fed infants? Clin Toxicol 50:1–14

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.html. Accessed 8 July 2015

Hudak ML, Tan RC, Committee on Drugs, Committee on Fetus and Newborn, American Academy of Pediatrics (2012) Neonatal drug withdrawal. Pediatrics 129: e540–e560

Ito S, Blajchman A, Stephenson M, Eliopoloulos C, Koren G (1993) Prospective follow up of adverse reactions in breast-fed infants exposed to maternal medication. Am J Obstet Gynecol 168:1393–1399

Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ (2006) Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet 368:704

Lam J, Kelly L, Ciszkowski C et al (2012) Central nervous system depression of neonates breastfed by mothers receiving oxycodone for postpartum analgesia. J Pediatr 160:33.e2–37.e2

Lefevere J, Allegaert K (2015) Question: is breastfeeding useful in the management of neonatal abstinence syndrome? Arch Dis Child 100:414–415

MacMullen NJ, Dulski LA, Blobaum P (2014) Evidence-based interventions for neonatal abstinence syndrome. Pediatr Nurs 40:165–172

Marsot A, Brevaut-Malaty V, Vialet R (2014) Pharmacokinetics and absolute bioavailability of phenobarbital in neonates and young infants, a population pharmacokinetic modelling approach. Fundam Clin Pharmacol 28: 465–471

Meador KJ, Baker GA, Browning N et al (2009) Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med 360:1597–1605

Meador KJ, Baker GA, Browning N et al (2014) Breastfeeding in children of women taking antiepileptic drugs. Cognitive outcomes at age 6 years. JAMA Pediatr 168:729–736

Ng CM, Dombrowsky E, Lin H et al (2015) Population pharmacokinetic model of sublingual buprenorphine in neonatal abstinence syndrome. Pharmacotherapy 35(7): 670–680

Nitsun M, Szokol JW, Saleh HJ et al (2006) Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. Clin Pharmacol Ther 79:549–557

O'Donnell M, Nassar N, Leonard H et al (2009) Increasing prevalence of neonatal withdrawal syndrome: population study of maternal factors and child protection involvement. Pediatrics 123:e614–e621

Ornoy A, Koren G (2014) Selective serotonin reuptake inhibitors in human pregnancy: on the way to resolving the controversy. Semin Fetal Neonatal Med 19:188–194

Patrick SW, Schumacher RE, Benneyworth BD et al (2012) Neonatal abstinence syndrome and associated health

care expenditures: United States, 2000–2009. JAMA 307:1934–1940
Patrick SW, Davis MM, Lehman CU, Cooper WO (2015) Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. J Perinatol 35:650–655
Pavek P, Ceckova M, Staud F (2009) Variation of drug kinetics in pregnancy. Curr Drug Metab 10:520–529
Pressler RM, Mangum B (2013) Newly emerging therapies for neonatal seizures. Semin Fetal Neonatal Med 18:216–223
Ramoz LL, Patel-Shori NM (2014) Recent changes in pregnancy and lactation labeling: retirement of risk categories. Pharmacotherapy 34:389–395
Reefhuis J, Devine O, Friedman JM et al (2015) Specific SSRIs and birth defects bayesian analysis to interpret new data in the context of previous reports. BMJ 351: h3190
Rivers CM, Olsen D, Nelson LS (2012) Breastfeeding and oxycodone. J Pediatr 161:174
Rowe H, Baker T, Hale TW (2013) Maternal medication, drug use, and breastfeeding. Pediatr Clin North Am 60:275–294
Saadeh RJ (2012) The Baby-Friendly Hospital Initiative 20 years on: facts, progress, and the way forward. J Hum Lact 28:272–275
Sachs HC, Committee on Drugs (2013) The transfer of drugs and therapeutics into human breast milk: an update on selected topics. Pediatrics 132:e796–e809
Salman S, Sy SK, Ilett KF, Page-Sharp M, Paech MJ (2011) Population pharmacokinetic modeling of tramadol and its *O*-desmethyl metabolite in plasma and breast milk. Eur J Clin Pharmacol 67:899–908
Sistonen J, Madadi P, Ros CJ et al (2012) Prediction of codeine toxicity in infants and their mothers using a novel combination of maternal genetic markers. Clin Pharmacol Ther 91:692–699
Siu A, Robinson CA (2014) Neonatal abstinence syndrome: essentials for the practitioner. J Pediatr Pharmacol Ther 19:147–155
Thomas SH, Yates LM (2012) Prescribing without evidence – pregnancy. Br J Clin Pharmacol 74:691–697
Turner SD, Gomes T, Camacho X et al (2015) Neonatal opioid withdrawal and antenatal opioid prescribing. CAMJ Open 13:E55–E61
Van den Anker JN (2012) Is it safe to use opioids for obstetric pain while breastfeeding? J Pediatr 160:4–6
Veiby G, Engelsen BA, Gilhus NE (2013) Early child development and exposure to antiepileptic drugs prenatally and through breastfeeding: a prospective cohort study on children of women with epilepsy. JAMA Neurol 70:1367–1374
Veiby G, Bjork M, Engelsen BA, Gilhus NE (2015) Epilepsy and recommendations for breastfeeding. Seizure 28:57–65
Verreault N, Da Costa D, Marchand A et al (2014) Rates and risk factors associated with depressive symptoms during pregnancy and with postpartum onset. J Psychosom Obstet Gynaecol 35:84–91
Wachman EM, Hayes MJ, Brown MS et al (2013) Association of OPRM1 and COMT single-nucleotide polymorphisms with hospital length of stay and treatment of neonatal abstinence syndrome. JAMA 309: 1821–1827
Zaijcek A, Giacoia GP (2007) Obstetric clinical pharmacology: coming of age. Clin Pharmacol Ther 81:481–482
Zimmermann-Baer U, Nötzi U, Rentsch K, Bucher HU (2010) Finnegan neonatal abstinence scoring system: normal values for first 3 days and weeks 5–6 in non-addicted infants. Addiction 105:524–528