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Chapter 26

Pregnant women, prescription, and fetal risk

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Abstract

Since the historical scandal of thalidomide in the 1960s, practitioners and future mothers are fearful of drugs during pregnancy. In-uterine exposure to drugs can induce major malformation of the fetus or even intrauterine fetal death. Prescribing drugs to a pregnant woman requires particular attention, and it is necessary to consider both the maternal needs and the proven and potential fetal risks. In this chapter, we review the mechanisms for medication transfer from mother to fetus, fetal risk according to pregnancy timeline, and the main dangerous drugs during pregnancy. We also focus on three prescription debates, which are relevant for neurodevelopmental disorder, because they each point to a paradigmatic situation—diethylstilbestrol, which shows transgenerational adversary effects; valproate, which impacts neurodevelopment as a whole; and antidepressants for which the adverse impact on neurodevelopment is still controversial given the impact of depression itself. Finally, we consider the implications for practice and toxicologic research to promote risk prevention.

INTRODUCTION

Physicians, practitioners, and the general population are fearful of drugs during pregnancy. The historical scandal of thalidomide in the 1960s has been followed by several other warnings that in utero exposure to drugs can induce major malformation of the fetus, or even intrauterine fetal death. Diethylstilbestrol in the 1980s and valproic acid, more recently, are drugs that have given rise to similar occurrences. These events highlight the need for a careful approach in this critical life stage.

Prescribing drugs to a pregnant woman requires particular attention and must consider both the maternal needs and the proven and potential fetal risks. Drug treatment of pregnant women is becoming more common: in occidental countries, about 30% of pregnancies are not anticipated, and a woman can find out she is pregnant while she is already under medical treatment. Moreover, first-time mothers are getting older and so are more at risk of being already diagnosed with a chronic disease. The situation where women undergoing medication wish to have children is now more common.

WHY WOULD THE FETUS BE AT RISK?

During pregnancy, normally there is no mixing of fetal and maternal blood. Vascular systems are separated by the placenta, a temporary tissue interface that allows exchanges between both blood compartments. As the pregnancy progresses, the surface area of the placenta increases and it becomes thinner. This transformation allows a larger quantity of nutrients to be transported and so facilitates the transit of drugs to the growing fetus. Some enzymatic activity is present in the placenta (e.g., prednisolone can be metabolized into prednisone), but its impact on drug metabolism is small. The term placental "barrier" is inappropriate. Except for high-weight molecules such as insulin, heparins, interferons, or

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anatoxins, most drugs can get through the placenta to various degrees (Elefant and Beghin, 2009). This means that the fetus can be exposed to exogenous substances with potentially dramatic consequences. In this chapter, we describe how the placenta functions, its transfer mechanisms, and the associated risks.

Function and histology

The placenta is the unique link between the mother and the fetus and is essential to the fetus' appropriate development. It is responsible for the nutrient supply and the removal of waste products from the fetus' blood. During the embryonic phase, the chorion is not perfused by maternal blood but by an extracellular fluid extracted from the plasma (Burton and Jaunaiux, 2001). Drugs and viruses may easily diffuse during organogenesis. From 10 weeks of pregnancy until delivery, maternal and fetal blood are separated by the so-called "barrier" composed of the fetal endothelium, the surrounding mesenchyma, and the trophoblast cells (discontinued cytotrophoblast and syncytiotrophoblast). From this point, molecules have to cross the barrier to get to the fetal blood compartment (Gude et al., 2004). With this barrier in place, the mother's and child's compartments are sealed and do not mix. However, some xenobiotics (such as drugs) can still pass through, using different mechanisms.

Transfer mechanisms

Passive diffusion

Passive diffusion is the main mechanism of exchanges through the placenta. It does not require any energy, is not overloaded, or prone to competitive inhibition. According to Fick's law, diffusion rate is proportional to both the surface and concentration, and inversely proportional to the placenta's thickness. Drugs with low molecular weight (<500 Da), which are fat-soluble and nonionized are more likely to diffuse (Audus, 1999), while binding to certain plasma proteins (albumin, alpha-1-acid glycoprotein) prevents other drugs from passing through. As explained earlier, the importance of this mechanism grows while the pregnancy progresses because the surface area of the placenta increases and becomes thinner. The increasing blood flow also facilitates the transfer of molecules from the mother's blood. Although maternal alpha-1-acid glycoprotein remains constant during pregnancy, the maternal albumin's concentration becomes lower. In contrast, the fetal alpha-1-acid glycoprotein and albumin concentration increase.

Active transport

Active transport requires energy to operate and allows molecules from the less concentrated compartment to "go against the flow." ATP hydrolysis or electrochemical gradient are used as energy providers. Many transporters are contained within the placenta, some facilitate the input of molecules (inflow pump) while others lower the fetus' exposure (outflow pump).

Inflow pumps ensure the transfer of necessary endogenous substances. *SERT* and *NET* are located on the apical pole of trophoblast cells and transport serotonin, dopamine, norepinephrine, and epinephrine (Ganapathy and Prasad, 2005). They are similar to neuron receptors and can be targeted by antidepressants and, eventually, stimulants such as cocaine and amphetamines. *OCT3* is located on the basal pole of the trophoblast and is involved in clearing catecholamines. It is inhibited by steroids and targeted by many molecules (cimetidine, prazosin). *OCTN2* and *OCTN3* are structurally close to *OCT1*. Located in the placenta, they are in charge of organic cations (*OCTN2* takes carnitine from the mother's blood to the fetus' blood). *OCTN3* has numerous exogenous substrates including nicotine, quinine, and fluoroquinolones (Yabuuchi et al., 1999), while beta lactam antibiotics are recognized by *OCTN2*. Methotrexate can interact with reduced folates transporter on the basal pole of syncytiotrophoblast cells (Ganapathy et al., 2004), while valproate, salicylates, and statins are recognized by the *MCT* transporter (responsible for lactate, pyruvate, and beta hydroxybutyrate intake). Finally, *ENT1* and *ENT2* (equilibrative nucleoside transporters), located on both poles of the trophoblast, transport nucleosides. They can carry several drugs such as cytarabine, gentamycin, and some antiretrovirals (Griffiths et al., 1997). *ENT1* is inhibited by dipyridamole, dilazep, and lidoflazine.

Outflow pumps have been discovered in the context of multidrug resistant cancer cells and are essentially ATP-Binding Cassettes (ABC). P-gp (P-glycoprotein) is located on the apical pole of syncytiotrophoblast cells. It causes the outflow of vincristine, vinblastine, and digoxine from the fetal blood compartment to the mother's (Ushigome et al., 2000). P-gp has the role of fetal protection against these molecules and their potential teratogenic effect. This role may be at its maximum in the sensitive period of organogenesis when P-gp is expressed more in the placenta (Gil et al., 2005). Several transporters of the multidrugs resistance-associated proteins family are also expressed in the placenta, and help in clearing metabolic waste products from the fetus (St-Pierre et al., 2000). Their role in protection of the fetus from drugs is being studied. Finally, breast cancer

resistance proteins (BCRPs) are highly expressed in the apical pole of trophoblast cells in human placenta and participate in transferring topotecan, PhIP, and glibenclamide out from the fetus' blood.

Other mechanisms

Facilitated diffusion, pinocytosis, and phagocytosis are less-used mechanisms for drug transfer. However, given the increasing use of monoclonal antibodies, pinocytosis deserves some description. Pinocytosis is an active mechanism involved in the transfer of microbiologic particles (viruses, bacteria) and macromolecules such as immunoglobulins (about 160 kDa). These immunoglobulins are mostly IgG, and constitute the passive immunity of children before they are old enough to be vaccinated. Generally, pinocytosis is a form of endocytosis in which small particles suspended in extracellular fluid are brought into the cell through the invagination of the lipid cell membrane (Elefant, 2012). The resulting vesicle can fuse with lysosomes in the cytoplasm to hydrolyze these particles. With regard to the immunoglobulins, the active Fc fragment of the molecule binds to a receptor called *FcRn* expressed at the apical pole of the syncytiotrophoblast cells (Kane and Acquah, 2009). The *FcRn-IgG* complex is protected from degradation and transported to the basal pole where the IgG is released to reach fetal capillaries (Szlauer et al., 2009). *FcRn* is expressed after the 13th week of amenorrhea and increases linearly over the course of pregnancy (Simister and Rees, 1985). IgG transfer is therefore at a maximum at the end of pregnancy, implying a better immunologic protection for children born at full term. Biologic therapy using monoclonal antibodies is in significant development. This emphasizes the importance of understanding pinocytosis and the structure of new IgG-modified treatments to both maintain the efficiency in treating the mother and protecting the fetus from potential consequences. For example, etanercept (fusion protein with a modified Fc fragment) and certolizumab (pegylated Fab fragment) are less likely to cross the placenta than infliximab and adalimumab (unaltered IgG1 molecules) (Mahadevan et al., 2013).

To summarize, the placenta is an essential organ, a "border structure," providing for the needs of the fetus and protecting it from several toxic substances with the outflow pump. Loopholes in the outflow process, passive diffusion of low molecular weight drugs, and unplanned transport of drugs recognized by inflow active mechanisms may weaken the barrier and expose the fetus to a number of risks.

PREGNANCY TIMELINE AND FETAL RISK

The embryo–fetal impact of an exogenous agent is different depending on the gestational age of the exposure. Three major periods are distinguishable: a brief early period of teratogenicity; a consecutive longer period of fetal risk until delivery; and the perinatal period.

Teratogenicity

Teratogenicity is the ability of a drug to cause fetal abnormalities or deformities. Organogenesis, the formation of organs, occurs during the first 2 months of pregnancy (until 10 weeks of amenorrhea) according to a precise chronological timeline. Teratogenic risk is at a maximum during this short period. The occurrence of a malformation depends on the drug, the genetic background of each embryo, and the moment of exposure during the organogenesis timeline. A drug with a risk of neural tube closure defect such as valproic acid or carbamazepine does not lead to this adverse effect if administered after neural tube closure (28 days postconception).

In the general population, 2% of newborns have a major malformation. Less than 5% of them are caused by medications or toxins. This means that every pregnancy has a base risk independent of drug intake. A teratogenic agent is defined by its potentiality and capability to increase the frequency of one or several malformations, such as cardiopathy with lithium, a drug for bipolar disorder (Fornaro et al., 2020) and skeletal and face damage with vitamin K antagonists, common anticoagulant drugs (Dhillon et al., 2018). Finally, it is important to note that no human teratogenic agent has a 100% chance to induce a congenital defect. Mycophenolate mofetil (an immunosuppressive drug) is one of the most powerful teratogenic agents known to date and causes deformities "only" in 25% of cases (Hoeltzenbein et al., 2012).

In the case of an accidental exposure to a drug in early pregnancy, future parents hope to be reassured that there is no risk of malformation. We must therefore remind them that in the best cases this exposure does not increase the base non-reducible risk of any pregnancy (about 2%). This medical communication is essential for human and medico legal aspects.

Fetal risk

The fetal phase begins after organogenesis, at the end of the second month of pregnancy, and lasts until delivery. Morphogenesis is almost complete. This long phase consists of fetal growing, and histologic and enzymatic maturation of systems formed during organogenesis

(central nervous system, kidneys, etc.). There is no fear of risk of malformation during this period. However, there is a risk of growth delay or permanent functional alteration of organs depending on the toxicity of the drug. Some of these fetotoxic effects can be diagnosed during pregnancy (such as decreased fetal movement, intrauterine fetal death, and hydramnios), while others are only noted after birth. Consequently, antihypertensive drugs affecting the renin angiotensin system cascade, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin 2 antagonists, have no teratogenic effect. However, exposure of the fetus after the first 3 months of pregnancy can cause severe kidney injury with consequences for renal function in utero or after birth (Weber-Schoendorfer et al., 2020). The same applies to all nonsteroidal antiinflammatory drugs, including aspirin above 500 mg/d, which act by inhibiting prostaglandin synthesis. They do not cause deformities but have fetal cardiovascular toxicity in utero with risk of ductus arteriosus constriction, intrauterine fetal death, and pulmonary arterial hypertension, and may cause renal dysfunction.

Other manifestations of these drug exposures can show up later in life. The risk of neurodevelopmental disorders (NDDs) such as autism spectrum disorders (ASDs) and attention-deficit hyperactivity disorder (ADHD) may be increased by valproic acid, a drug used for epilepsy or bipolar disorder (Veroniki et al., 2017; Christensen et al., 2019), and risk of cancer is increased with diethylstilbestrol, a synthetic hormone used to prevent miscarriages.

Neonatal risk

During the whole period of pregnancy, the maternal organism eliminates the medication for the fetus. At childbirth, the newborn itself has to eliminate the drugs that passed through the placenta (and eventually through breast feeding). But metabolic and excretion mechanisms are still partially immature and drug elimination takes generally longer than usual, particularly in the case of prematurity. The newborn can be impregnated with a drug taken by the mother several days before delivery. The symptoms, mostly temporary, are expected effects of the molecule in adults or side effects. To illustrate, β-receptors blockade in a newborn whose mother took β-blockers at the end of pregnancy can result in hypoglycemia and/or neonatal bradycardia (Cissoko et al., 2005), and a newborn whose mother took benzodiazepines could be sedated (Bavoux, 2020). Less frequently, withdrawal symptoms can occur in newborns when mothers have had long-term exposure to molecules responsible for withdrawal syndromes in adults, such as antidepressants (selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs); Alwan et al., 2016). Symptoms show up several days after birth, depending on the specific molecule's half-life in blood.

DANGEROUS DRUGS DURING PREGNANCY

Drugs with a proven hazardous effect to date are listed in Table 26.1 (Mellin and Katzenstein, 1962; Brunskill, 1992; Dawson et al., 2014). This list is regularly updated on the French website www.lecrat.fr. Other updates can

Table 26.1

Dangerous drugs during pregnancy

Drugs associated with teratogenicity	
A teratogenic drug is likely to cause malformations in children whose mothers have been treated during the pregnancy. The period when teratogenic risks are the most important is during the first 2 months of pregnancy. In the general population, about 2% of children are born with a major malformation. A teratogenic drug increases this overall frequency, or only that of a specific type of malformation	
Teratogenic drugs to be prohibited during at least the first 2 months of pregnancy, and if possible beyond, unless exceptionally indicated	
Valproic acid	Tomson et al. (2018)
Acitretin	Lammer et al. (1985)
Diethylstilbestrol	Hoover et al. (2011)
Isotretinoin and other retinoids (alitretinoin)	Lammer et al. (1985)
Misoprostol	Gonzalez et al. (1998)
Mycophenolate	Hoeltzenbein et al. (2012)
Thalidomide	Mellin and Katzenstein (1962)
Testosterone and danazol (effect only on female fetuses)	Brunskill (1992)
Antimitotic drugs (methotrexate, cyclophosphamide, …)	Dawson et al. (2014)
Teratogenic drugs for use during pregnancy in the absence of a safer therapeutic alternative	
Lithium salts	Fornaro et al. (2020)
Carbimazole	Song et al. (2017)
Vit K antagonists (warfarin, acenocoumarol, fluindione)	Dhillon et al. (2018)
Carbamazepine	Tomson et al. (2018)
Phenobarbital	
Topiramate	
Drugs associated with a fetal risk	
From the beginning of the third month of pregnancy, organogenesis is over. Some drugs are specifically dangerous during this period due to more or less severe irreversible fetal or neonatal effects, without malformative effects, and therapeutic alternatives exist	

Table 26.1

Continued

Fetotoxic drugs to be prohibited during fetal life	
Nonsteroidal antiinflammatory drugs (NSAIDs) and selective Cox-2 inhibitors (ibuprofen, ketoprophen, nimesulide)	Li et al. (2018)
Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-2 antagonists (captopril, enalapril, losartan)	Shotan et al. (1994)
Fetotoxic drugs for use during fetal life in the absence of a safer therapeutic alternative	
Antibiotics of the cyclin class	Muanda et al. (2017)

Modified from Eléfant E (2020). Prescrire chez la femme enceinte. Rev Prat 70(1): 11–16.
List from the Centre de référence sur les agents tératogènes (CRAT), www.lecrat.fr (updated March 13, 2019).

be found through the European Network of Teratology Information Services (https://www.entis-org.eu/) or the Organization of Teratology Information Specialists (https://mothertobaby.org/about-us/). These drugs are classified depending on the risk they increase during pregnancy and the benefit they provide in terms of maternal health. Later in this chapter, we focus on three kinds of drugs with specific interest in neurodevelopment.

Drugs associated with teratogenicity

Some of these agents such as isotretinoin (used in severe acne), acitretin (used in ichthyosis), and other retinoids are strictly forbidden during pregnancy because they provoke a teratogenic effect, and they do not serve vital medical needs (Lammer et al., 1985; Mondal et al., 2017).

For other molecules, the therapeutic benefit and the possibility of monitoring the pregnant woman to detect malformations allows their prescription during all stages of pregnancy, despite the risk of causing a teratogenic effect, if no safer and equally effective alternative is available. For example, an anticonvulsant such as carbamazepine should not be prescribed at the beginning of pregnancy due to the risk of neural tube closure defect (anencephaly or spina bifida in about 1% of cases) (Tomson et al., 2018), but this drug can be reintroduced after the first trimester. If discontinuation is not possible for medical maternal reasons, the treatment may be continued during organogenesis with strict prenatal echographic monitoring of the neural tube.

The challenge of finding a safer and equally effective alternative exists with other teratogenic drugs. It is almost impossible to find a substitute for a vitamin K antagonist used as oral anticoagulant in a patient with prosthetic cardiac valvula (risk of valvular thrombosis). Despite the teratogenic risk, carbimazole cannot be suspended in a patient with hyperthyroidism who does not tolerate propylthiouracil because of a history of agranulocytosis. Similarly, valproic acid requires a specific focus and is detailed in the section "Valproic acid". Despite their known teratogenic effect, these drugs can be used during pregnancy if there is a therapeutic benefit and if prenatal monitoring is possible.

Drugs associated with a fetal risk

These drugs are specifically dangerous during the fetal period due to more or less severe irreversible fetal or neonatal effects rather than malformative effects. First, switching to a less dangerous and equally effective therapeutic alternative should be considered. Only nonsteroidal antiinflammatory drugs (NSAIDs) and ACE-I/angiotensin 2 antagonists are strictly forbidden until after the 24th week of pregnancy for NSAIDs and after the 15th week of pregnancy for ACE-I/angiotensin 2 antagonists (Shotan et al., 1994). They have severe irreversible effects on the fetus; also several other less toxic alternative molecules are available. There is no dose–response relationship; irreversible cardiovascular effects and intrauterine fetal death can occur with low dose, short lasting doses, and even a single dose of NSAID. The risk is maximum when near-term exposure.

For other treatments, the existence of a suspected or proven fetal or neonatal effect is not sufficient to contraindicate the prescription of a molecule to a woman who needs to be treated. We should consider maternal needs and share our decision with the other clinicians in charge of the management of mother and child (doctors, midwifes, and pediatricians).

The strategy of lowering posology or suspending the prescription of a chronic medication near term to lower the child's impregnation with pharmacologic agents is not always a good idea and should not be systematically performed. The mother's needs must be balanced with protection of the fetus. The postpartum period is particularly difficult for some women with chronic diseases that may worsen due to physiologic modifications (some psychiatric diseases, inflammatory diseases, system diseases, and multiple sclerosis).

DRUGS OF SPECIFIC INTEREST FOR NEURODEVELOPMENT

Diethylstilbestrol

Diethylstilbestrol (known as Distilbène® in the media) is a synthetic estrogen developed in 1936 and regularly

used from 1946 to the 1970s for women to prevent miscarriage and premature labor. The mechanism hoped for was to correct the steroid deficiency in early miscarriage. The drug was released before any clinical trial had been conducted and was only based on the misinterpretation of uncontrolled and biased studies. In 1953, in a large placebo controlled trial, it was shown not to be superior to placebo (Dieckmann et al., 1953).

Diethylstilbestrol led to serious consequences for mothers and children and caused a major scandal with impact on the history of medicine (Hoover et al., 2011; Fénichel et al., 2015). The history of complications started with the observed increased risk of cervicovaginal clear cell adenocarcinoma in very young women exposed to diethylstilbestrol in utero in 1970 (Herbst and Scully, 1970), which led to the ban of the drug in many countries after 1972. Ten million pregnant women had taken the drug. Starting from 1977, for women, and 1990, for men, reproductive tract malformations such as "Diethylstilbestrol uterus," T-shaped uterus, and hypospadias were identified (Exposed women frequently suffered from infertility even in the absence of morphologicabnormalities). These teratogenic and fetotoxic effects have all been reproduced in animal models with fetal or perinatal exposure. Diethylstilbestrol also increases the risk of having metabolic, cardiovascular and/or bone diseases; the fetal programming (Barker, 2003) of later diseases depends on gestational age and the kind of fetal exposure.

As pointed out above, diethylstilbestrol increases the risk of tumors and this risk persists 50 years after the first prescriptions: the second-generation daughters still show a threefold risk of developing breast cancer (Palmer et al., 2006). Even further from the first generation that was exposed, the third generation of grandsons have an apparent increased risk of hypospadias according to at least five different studies to date (Klip et al., 2002; Kalfa et al., 2011). Other nongenital malformations are suspected in third generation exposed individuals (Titus-Ernstoff et al., 2010). This suggests a possible transgenerational transmission without mutation (probably an epigenetic modification) added to the long-term fetal programming of an adult disease.

The exposure window makes clearer the mechanisms involved, explaining a greater toxicity after in utero exposure than in treated women. Diethylstilbestrol estrogen can pass cross the placenta and disrupt fetal development. As a sex steroid, diethylstilbestrol may modify the development and differentiation of the genital tract during the fetal period. It is also possibly linked with carrier proteins in a less effective way than in adults receiving the drug. Detoxification enzymes and blood–genital barriers might also be immature at the time of exposure. The fixation of diethylstilbestrol (or other estrogen-mimetics) on different receptors depending on the dose (*ER-alpha*, *ER-R*, or *NROb-2*) can explain the opposite effect observed. Transgenerational transmission could be explained by epigenetic mutation of genes involved in structural differentiation of the reproductive tract such as HOX genes (Ma et al., 1998) or genes involved in susceptibility to cancer such as the lactoferrin gene (Li et al., 1997), affecting the expression of estrogen-regulated genes (c-*jun*, *c-fos*, *c-myc*, *BALC*, *BCL-2*, *BCLX*). The delayed manifestation of the modification in an age period when the gene should activate/deactivate makes an epigenetic mechanism more likely than a mutation. According to animal studies that suggest a transmission up to the fifth generation of mice after the first in utero exposition, epigenetic transmission despite many reset processes may be carried out by small noncoding RNAs or microRNAs (Rassoulzadegan et al., 2006).

Synthetic hormones do not necessarily have the same properties as native hormones. The case of diethylstilbestrol strengthens the need for evidence-based prescription and careful studies of drugs administrated to pregnant women. Animal models and in vitro models are discussed later in this chapter. In the neuropsychiatric field, diethylstilbestrol's story has contributed to an acknowledgement that the fetal environment has a role to play in the development of chronic diseases and even has a transgenerational emphasis.

Valproic acid

Valproic acid is a very efficient drug used both in neurology and psychiatry. It crosses the placenta with similar or higher concentrations in the blood of the fetus than in the mother's blood. The risk of induced malformation is high (10%–15%) and makes it the most teratogenic anticonvulsant in humans to date (Werler et al., 2011). The effect is both morphologic and functional, is dose dependent, and starts from a minimum dose (Tomson et al., 2011). The polymalformative syndrome consists of cardiopathy, neural tube closure defect (essentially spina bifida), hypospadias and renal malformations, cleft palate or cleft lip, craniostenosis, limb malformations, and characteristic facial dysmorphia. Previous pregnancies with valproic acid-induced malformations increase the risk of recurrence. Prenatal exposure in animal models supports the findings in humans.

In addition to an increased risk of congenital malformations, valproic acid in pregnancy is associated with several neurodevelopmental outcomes ranging from intellectual defects with lower global IQ, mean IQ being 10 points lower, verbal IQ being the most affected with 20%–40% of children with verbal IQ below 80 (Meador et al., 2009), to psychiatric disorders emerging in childhood. Along with other environmental

chemicals (drugs such as thalidomide, misoprostol, or toxins like alcohol, cocaine, and toxic metals) exposure to valproic acid during pregnancy has been associated with developmental delays, and an increased risk of NDD including ASDs (Christianson et al., 1994). The risk seemed to increase in some studies when valproic acid was associated with other antiepileptic drugs (Rasalam et al., 2005). In a large population-based study on Danish people, Christensen et al. (2013) found 508 children exposed in utero to valproic acid and 2136 to other anticonvulsant drugs over a total of 655,615 eligible children. An increased risk (Hazard ratio 3.0 for ASD and 4.9 for childhood autism) was found for those exposed to valproic acid even after adjusting for potential confounding bias (mother disorders, age, parity, toxins). There was no statistically significant increase of risk with another anticonvulsant used alone. The risk was high for the first trimester of exposure as well as later exposures. More recently, using the same methodology (580 exposed to valproate out of 913,302 eligible children), Christensen et al. (2019) also showed an increased risk of ADHD. Of children exposed to valproic acid 8.4% developed ADHD while only 3.2% of others had ADHD (Hazard ratio 1.48). The absolute 15-year risk was raised to 11.0% for exposed children and only 4.6% for others. Exposure after the first trimester accounted for very few women and the small group showed no statistically significant increase of the risk for late exposures, although it could not be ruled out. Again, no direct association was found between ADHD and other anticonvulsant drugs.

A study of the offspring of rodent models after exposure to valproic acid during pregnancy showed behaviors compatible with NDD and ASD. They showed anatomical alterations—reduced number of cerebellar Purkinje cells, damage to cranial nerve nuclei (Ingram et al., 2000), and enhanced synaptic plasticity of the prefrontal cortex (Sui and Chen, 2012). In 2014, zebrafish embryotoxicity tests confirmed that valproic acid was the most potent neurotoxic drug of all antiepileptic drugs tested.

Ideally, since data indicate that a lot of pregnancies are unplanned, valproic acid should not be used in women of childbearing age and must not be taken by pregnant women. Some countries have implemented precautions, such as a signed form, justification of prescription, and/or specialist only prescription, for prescribers to avoid using this drug; but in some cases, there is no other option offering the same benefit. In lithium-intolerant women of childbearing age, atypical antipsychotics followed by conventional neuroleptics or oxcarbamazepine should be considered. If only valproic acid can be used because of the ineffectiveness of alternatives, e.g., the woman must be informed of the risk associated with pregnancy and must use birth control on a permanent basis. Pregnancy risk must be assessed with the patient and any pregnancy plan should be supervised. In the case of an unexpected pregnancy during treatment, valproic acid must be discontinued and treatment moved to another molecule, followed by close echographic tracking for malformations, and then controlled by child specialized monitoring (with neurodevelopmental medical support and reeducation if needed).

Antidepressants

In contrast to the impact of valproate or diethylstilbestrol on fetal development, the impact of antidepressants is more difficult to assess given the impact of depression itself. Between 9% and 14% of pregnant women occasionally show one symptom of depression (Evans et al., 2001). SSRIs increase extracellular serotonin and are used as first line treatment of adult depression because they show a good tolerance and a safer profile than tricyclics. All antidepressants are able to cross the placenta, raising concerns about possible adverse events for the fetus. We have seen earlier that antidepressants fix the same kind of receptors in the placenta as in brain. Estimating the risk of such transfer is important to the risk–benefit balance of the prescriptions.

There is a possible risk of arterial hypertension or preeclampsia in women taking antidepressants during pregnancy (especially with SNRIs). However, exposure during organogenesis does not seem to induce any malformative syndrome. Antidepressants do not increase prematurity rate either. Withdrawal or impregnation syndromes in children after delivery happen in about 30% of cases; neonates can show respiratory distress, tachypnea, tremors, excitability, and sleep, tonus, or alimentation problems. They are generally transient, short lasting and benign, and they seem to be facilitated by an abrupt interruption of antidepressants before childbirth. There are conflicting data in the literature about an increased risk of neonatal pulmonary hypertension for fetuses exposed to SSRI antidepressants during the second half of gestation. This area needs further research.

Several studies have suggested an increased risk of ASD of about twofold (OR = 2.2) (Croen et al., 2011), if the mother took an SSRI treatment the year before delivery, with a substantial effect for an exposure in first trimester of pregnancy (OR = 3.8). Rai et al. (2013) found an increased risk of ASD (OR = 3.34), especially without intellectual disability, in a Swedish case control study of 4429 children with ASD and 43,277 control children. This association was found in the subsample of women with a history of medical depression (this variable also being associated with an increased risk of ASD, OR = 1.49, unlike paternal depression). Gidaya et al. (2014) and Harrington et al. (2014) also examined

huge cohorts with similar outcomes. The meta-analysis of Man et al. (2015) supported these results. However, more recent studies are conflicting; several recent papers have not established the increased risk after adjusting for maternal depression, magnifying the specific role of the disease itself (Hviid et al., 2013). The same uncertainty exists regarding ADHD, with an increased risk in case of prepregnancy exposure to antidepressant but not with prenatal exposure (Castro et al., 2016). In both cases, the size of the increased risk, if any, seems to be very low (antidepressant use during pregnancy explained less than 1% of ASD cases in Rai et al. study). To date, it is not possible to reach a conclusion about an increased independent risk of ADHD or ASD after fetal exposure to antidepressants. Recently, a possible association between in utero exposure to antidepressants and intellectual disability has been explored by Viktorin et al. (2017). After adjustment for confounding factors such as parental age and mother's psychiatric disorder, the study did not find evidence of an association between intellectual disability and maternal antidepressant medication use during pregnancy.

A first general recommendation for antidepressants would be to consider the planning and possible delay of the pregnancy, if a woman suffers from an acute depression requiring high dose of psychotropic drugs. Nonmedicated approaches should be discussed, if possible, as an alternative to treat depression or anxiety disorder. When there is no alternative, most antidepressant drugs are allowable during pregnancy, and a pregnant woman must never be undertreated or untreated. Relapses can have dramatic consequences during the fragile period of pregnancy. As usual, monotherapy is preferred to polytherapy when possible, at the lowest effective dose. The dose needed may increase in the course of pregnancy because of physiologic modifications. Antidepressant drugs should not be abruptly interrupted during pregnancy. A disregard for maternal depression results in an increased risk of negative outcomes during pregnancy (prematurity, low birth weight) and after delivery (mother–child bond) (Suri et al., 2014). Breastfeeding must be anticipated by clinicians and sertraline or paroxetine might be preferable as a prescribed antidepressant.

WHAT SHOULD BE DONE TO LIMIT RISK?

Prescribing to pregnant women

As for any adult patient, prescribing to pregnant women begins with an assessment of the benefit expected from the treatment. The different available therapeutic options are considered with regard to gestational age, past medical history, and medications previously taken. The goal is to find a balance between the medical needs of the mother on the one hand and protection of the expected child on the other. Prescriptions should be limited to necessary ones, with strong justification. Unfortunately, the fear of drugs in pregnant women may lead to inappropriate care such as abrupt suspension of a necessary treatment or its substitution with a less efficient drug. In various chronic or acute diseases such as epilepsy, psychosis, asthma, prosthetic cardiac valvula, lupus, glaucoma, and infections, this approach may have consequences for the patient in the short or medium term. To put it another way, many pregnant women suffer from a loss of opportunity with regard to medical diagnosis (radiologic explorations in particular) and therapeutics, with a potential health impact sooner or later. It is important to note the danger of this attitude.

Because no safer and equally effective therapeutic alternative is available, some drugs with proven (or suspected) risk for the fetus are continued or prescribed because they are essential to the mother (Muanda et al., 2017). In these situations, every effort must be focused on detecting potential risks—specific prenatal diagnosis (ultrasound or magnetic resonance imaging) and/or neonatal monitoring. Once healthcare professionals are confident with this strategy, it must be discussed with the pregnant patient. Future mothers often decide to interrupt their treatment to avoid potential fetal injuries for which they would feel responsible. Unfortunately, this understandable reaction often leads to worsening of the disease during pregnancy, which requires more difficult and aggressive treatments than the usual chronic prescription. Patients should be informed of this risk. This emphasizes the utility of preconception consultations for women of childbearing age who are taking chronic medication for a chronic disease and also wish to have a child. Ideally, preconception consultations should occur before they become pregnant.

Studying fetal risk for novel drugs

While a lot of scandals have originated from case series and retrospective studies for drugs that were considered safe, the Cochrane database lists clinical trials conducted in pregnant women with prospective data collection. The number is limited, and they are essentially studies regarding prescriptions for pregnant women (analgesics, antibleeding, and treatment of various pregnancy disorders). Another way to study fetal risk for novel drugs is to evaluate the transfer of these drugs in laboratory models. Their common advantage is that they bypass ethical and methodological boundaries, while they are limited by not taking into account physiologic and biochemical variables of the mother, placenta, and fetus, nor their evolution over the time of pregnancy.

Ex vivo model

The ex vivo model of the perfused cotyledon (Gavard et al., 2009) consisted of a perfusion study of a preserved cotyledon from a full-term placenta. Antipyrine diffusion was used to verify the quality of the cotyledon as it is known to diffuse freely across the placenta. This model was used to determine the transfer of substances and the effect of endogenous and exogenous chemicals on perfusion pressures and transports and to measure the release of endogenous substances in fetal and maternal blood. Inhibiting a specific transport protein and evaluating the transfer of drugs allows identification of the role of this protein and clarifies the risk–benefit balance for the fetus as a result of the mother's therapeutics.

In vitro model

The in vitro model uses tissue fragments and cell lines to assess the existence of transport or metabolism mechanisms in the placenta (Bourget et al., 1995). Tissues explants from placenta or villi conserve the microarchitecture, cell interactions, and paracrine communication. It is possible to use tissues from all term placenta. Syncytiotrophoblast cell culture offers the possibility of studying cell and molecular mechanisms of transport by measuring the capture of radioactive substances. It is possible to express specific transporters on isolated trophoblasts and determine the possible interactions between xenobiotics and natural substances. Isolated trophoblasts are also used for the study of drug transport and gene expression regulation in syncytium formation (Frank et al., 2001). Cell lines derived from human choriocarcinoma (BeWo, JAr, and JEG) have similarities with trophoblasts from villi in terms of morphology, biochemical markers, and hormonal secretion (Liu et al., 1997). They are regularly used to study the placental barrier and transport mechanisms. Finally, vesicles from villi membranes are used to study fetal and mother transport mechanisms separately (Hemmings et al., 2001).

In vivo model

The in vivo model involves measuring a drug's concentration ratio between the mother's blood (peripheral vein at placenta delivery) and fetal blood (from umbilical cord). It reflects the transfer index in vivo but does not help in understanding the mechanisms involved (Bourget et al., 1991).

To illustrate, glibenclamide is a hypoglycemic sulfonylurea as effective as insulin to control gestational diabetes. As mentioned earlier, insulin does not cross the placental barrier but its inconvenience comes from being an injectable medication. Glibenclamide in an oral drug for which the physicochemical characteristics raise concerns about fetal transfer, but when measured, Glibenclamide is undetected in fetal blood in the umbilical cord 4 h after the last intake of the mother (in vivo model) (Langer et al., 2000). The perfused cotyledon method shows a strong fixation of glibenclamide to albumin, and the existence of an efflux pump since there is an active transfer from the fetal to the mother's side (ex vivo model) (Nanovskaya et al., 2006). Finally, BCRP receptors found in trophoblasts and vesicles from villi membranes (in vitro model) have been involved in this transfer because their ex vivo inhibition shows an increased transfer to the fetal compartment (Pollex et al., 2008).

Informing practitioners

Finally, we believe that there is a need for informing practitioners and updating knowledge regarding drugs and fetal risk. In many cases, the risk is acknowledged years after the first use of a drug. Some practical clinical situations are given in Table 26.2. In all circumstances and

Table 26.2

Prescribing to pregnant women: practical clinical situations (Eléfant, 2020)

A woman has been taking medication and finds out she is pregnant	Do not scare her (only a few medications require medical termination of pregnancy) Determine for each drug the nature, posology, indication, and date of exposure from the beginning of pregnancy Examine the available documentations: pharmacologic, embryologic, and epidemiologic Consult the CRAT (www.lecrat.fr), ENTIS, OTIS
A pregnant woman needs to be treated	Justify the validity of the pharmacological prescription Choose the safest known treatment regarding gestational age Do not undertreat pregnant women Assess possible interaction between the disease and pregnancy Program monitoring of mother and child Make sure all clinicians involved in the situation of the mother and the child coordinate

Continued

Table 26.2

Continued

A woman treated for a chronic disease (cardiopathy, diabetes, epilepsy, rheumatologic disease, psychiatric disorder, …) wishes to have a child	Program a preconception consultation if possible, to reevaluate the necessity and choice of the treatment for the disease
A woman gives birth to a child with a malformation and/or suffering from a nonmalformative neonatal disease	Obstetrical anamnesis finds out an exposure to a drug: (1) get a specialized and detailed medical report of the malformation or the neonatal disease; (2) get information about the course of the pregnancy, the delivery; (3) look for a different etiology, especially genetic (the most frequent); (4) discuss a specialized consultation; and (5) provide feedback to a recording system (CRAT in France, ENTIS, OTIS, pharmacovigilance networks)

CRAT, Centre de référence sur les agents tératogènes, www.lecrat.fr; *ENTIS*, European network of teratology information services; *OTIS*, Organization of teratology information specialists.

for all patients, the decision process must consider objective elements to evaluate the risk–benefit balance. The challenge is greater in pregnant women because the final decision involves not only the woman but also the child, which generally has no direct benefit from the treatment. This difficult decision is taken both by the clinician and the future parents and still regularly leads to questionable prescriptions. The objective is therefore to think of the best therapeutic strategy with regard to good clinical practices for each pathology and a medical choice based on available evidence. These choices must be adapted to the situation of a pregnant women when data are available; in the best scenario we could build a drug hierarchy depending on certain criteria (such as gestational age) to decide which drug to use. If data from pregnant women are missing, prescription will only rely on the absolute necessity of the medication.

To improve current practice, teratogenicity risk awareness should be increased among women of childbearing age with epilepsy and other medical conditions, and among physicians. Pregnancy requires a return to the basics of medical prescription, a constant questioning of knowledge and therapeutic approaches, and permanent caution.

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