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Review

Pharmacological treatment for cardiovascular disease during pregnancy and lactation

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ABSTRACT

Maternal circulatory dynamics change drastically during pregnancy and delivery. Therefore, pregnancy with concomitant cardiovascular disease has risks, even for maternal death, in severe cases. This condition has tended to increase with advances in medical care and an increase in the age of pregnant women. Drug therapy during pregnancy and lactation should be administered if it is judged that this is necessary to improve the maternal pathology despite a risk of adverse effects. Fetuses and infants are exposed to maternal drugs, which is a specific concern in drug therapy for pregnant and lactating women. Care is needed because of the risk of adverse effects of teratogenicity in the organogenesis period and fetal toxicity thereafter. However, unstable maternal circulatory dynamics also inhibit fetal development and increase the risk of premature delivery, and stabilization of maternal physiologic condition by drug therapy often gives benefit to fetuses indirectly. Therefore, detailed knowledge of drug therapy during pregnancy should be acquired to manage the condition appropriately. Caution is also needed in using some obstetric drugs, such as tocolytic agents, which influence maternal circulatory dynamics. Therefore, drug therapy during pregnancy and lactation should only be used after full consideration of its benefit and possible harm to the mother and child, and after obtaining consent from the patient after giving a sufficient explanation. In this report, we review drug therapy for pregnant and lactating women with concomitant cardiovascular disease.

Contents

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Introduction

Various physiological changes occur in the pregnant maternal body. Changes in circulatory dynamics mainly include: (i) increase in circulating plasma volume, (ii) increase in heart rate, (iii) reduction of vascular resistance, (iv) hypercoagulability, and (v) increase in vascular wall vulnerability. Accordingly, in pregnancy with cardiovascular complications, the incidences of heart failure, arrhythmia, thromboembolism, and aortic dissection are increased. Drug therapy is necessary for treatment and prevention of these perinatal cardiovascular complications in many cases. One registry study reported that one third of pregnant women with heart disease used cardiac medication during their pregnancy, which was associated with an increased rate of adverse fetal events [1]. However, there is little information concerning drug therapy during pregnancy and lactation. The section on pregnant and lactating women in package inserts of drugs is written based on the results of overdose drug testing in reproductive animals, but application of results from animal experiments to humans is limited. Judgment based on experience in humans is more appropriate, but epidemiological studies in pregnant and nursing mothers are limited and it is difficult to include the results of such studies in package inserts.

The risk of obstetric complications, such as threatened preterm labor (TPTL) and atonic bleeding, also increases in pregnancy with cardiovascular disease [2]. However, some drugs for these obstetric complications influence maternal circulatory dynamics, and therefore, it is important that physicians provide appropriate information and treatment based on knowledge of the benefits and potential harm to the mother and child of drug administration during pregnancy and lactation.

Drugs used during pregnancy

The influence of drugs used during pregnancy on fetuses is roughly divided into two types. The embryonal stage (about 4–10 weeks of gestation) includes the organogenesis period. The first 2 weeks after conception are considered as the time of 'all-or-nothing' phenomenon; a concept in which early embryonic exposure before organogenesis either results in embryonic death or no adverse outcome. Five to nine weeks of gestation is the most important period with regard to structural abnormality and corresponds to the critical period of most major anomalies. The incidence of major anomalies in the absence of complications and drug use is about 3% [3,4], and when this incidence rises due to use of a drug in early pregnancy, the drug is considered to be teratogenic. The problems with drug use in the fetal stage (after about 10 weeks of gestation) include functional disorder, such as developmental disability, fetal growth inhibition, and aggravation of the intrauterine environment, such as oligohydramnios. These adverse effects of drugs that are ingested by the mother and act on the fetus after transfer through the placenta are referred to as 'fetal toxicity'. Placental transfer increases as the maternal blood level rises, the molecular weight of the drug decreases, and the tendency for ionization decreases, leading to high fat solubility. The decision to use a drug during pregnancy should be determined with consideration of the gestational age, the teratogenicity and fetal toxicity of the drug, and the treatment effect on the maternal body. Mothers are anxious about the influence of drugs on fetuses, and a sufficient explanation and obtaining consent are important for use of any drug.

Drugs for heart failure

After pregnancy is established, the circulating plasma volume and cardiac output gradually increase and reach about 1.5 times those in the non-pregnant state at 28–32 weeks of gestation. At the time of delivery, 200–400 mL of uteroplacental blood is transferred to the systemic circulation in each uterine contraction and the cardiac output further increases. The inferior vena cava is released from compression by the enlarged uterus immediately after delivery, and blood circulating in the uterine artery returns to the heart with uterine contraction, causing a sharp increase in venous return. Normalization of the volume load takes about 3–6 weeks, or longer. Against this increase in volume load, development of heart failure and relatively low cardiac output may occur in patients with stenotic lesions, pulmonary hypertension, and deteriorated cardiac function. A study of perinatal heart failure showed that the onset time of heart failure was 20–30 weeks of gestation in many cases with organic heart disease, but at delivery to 1 month after delivery in cases with peripartum cardiomyopathy and ischemic heart disease [5].

Diuretics, carperitide, and inotropic agents, including catecholamines, can be used to treat acute heart failure during pregnancy. In the use of diuretics for chronic heart failure, there are concerns of excess diuresis-induced reduction of uterine circulation, oligohydramnios, fetal diuresis-induced dehydration, and abnormal electrolyte balance. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are contraindicated because these drugs cause fetal renal hypoplasia and oligohydramnios [6]. Aldosterone antagonists are considered safe at a normal dose. The characteristics of the main drugs for heart failure in pregnancy are shown in Table 1.

Timing of delivery in pregnant women with acute heart failure is difficult. Mothers in shock to their vitals may need immediate delivery. However, the systemic circulation and the cardiac output further increase at the time of delivery. In cases where maternal vitals are stable and pregnancy-related volume load is a cause of heart failure, volume reduction before delivery by diuretics or other drugs may have the effect of preventing further exacerbation of heart failure (Fig. 1).

Drugs for arrhythmia

Arrhythmia increases during pregnancy, including benign cases that do not require therapeutic intervention, with increases in circulating plasma volume, heart rate, and sympathetic nerve activity; variation of blood electrolyte and hormone levels; and myocardial extension-associated instability of myocardial electrical potential. Thus, arrhythmia is the cardiovascular event that is most frequently observed in pregnant and nursing mothers, and is likely to occur in the 2nd trimester of pregnancy (14–17 weeks of gestation) and 3rd trimester (after 28 weeks of gestation) [7]. Sinus arrhythmias including sinus tachycardia and supraventricular/premature ventricular contraction are also common in an otherwise healthy pregnancy [8]. Many pregnant and nursing mothers complain of symptoms of palpitation and vertigo, but this is a perinatal characteristic that is not necessarily due to arrhythmia [9].

Arrhythmia is likely to recur in the perinatal period in women with a history of arrhythmia before pregnancy [10]. The rate of complications in neonates, such as premature birth and low birth weight, is high in cases with atrial fibrillation and atrial flutter, to which careful attention should be paid [11,12]. For cases indicated for catheter ablation, pacemaker and implantable cardiac defibrillator, these procedures should preferably be performed before pregnancy. Arrhythmia during pregnancy is treated similarly to that in non-pregnant cases, but drug selection should include consideration of the influence on the fetus. Details of oral administration of anti-arrhythmia drugs during pregnancy and lactation are shown in Table 2. Intravenous administration of adenosine triphosphate (ATP) and electrical defibrillation for

Table 1
Drugs for heart failure in pregnancy and lactation.

Drugs	Use in pregnant women in package insert	Evaluation of use during pregnancy[a]	Influence on outcome of pregnancy and points of management	Transfer to breast milk	Evaluation of use while breastfeeding[b]
Milrinone	Benefits administration	●		+ (animal data)	–
Pimobendan	Benefits administration	●	Risk of growth retardation	+ (animal data)	–
Carperitide	Benefits administration	●	Risk of growth retardation	+ (animal data)	–
Dopamine	Benefits administration	●		ND	○
Dobutamine	Benefits administration	●		ND	○
ACE inhibitors	Contraindicated	×	Risk of oligohydramnios, growth retardation, lung hypoplasia, intrauterine fetal death	+	○
ARB	Contraindicated	×	Risk of oligohydramnios, growth retardation, lung hypoplasia, intrauterine fetal death	+	●
Spironolactone	Benefits administration	●	Antiandrogenic effects (feminization) in male rat were reported	+	○
Hydrochlorothiazide	Benefits administration	○	Risk of decreased uteroplacental blood flow, growth retardation, oligohydramnios	+	○ (milk production can be reduced with large dose)
Furosemide	Benefits administration	●	Risk of decreased uteroplacental blood flow, growth retardation, oligohydramnios	+	○ (milk production can be reduced with large dose)

ND, no data; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
Benefits administration: use during pregnancy only if the potential benefit outweighs the potential risk to the fetus.
[a] Definition of evaluation during pregnancy
○ Compatible: safety suggested in an epidemiological study.
● Suggest low risk: human data are limited, but the drug is considered safe based on similar drugs and experience.
▲ Suggest moderate to high risk: risk cannot be ruled out because human data are absent or limited and experience is insufficient.
×Contraindicated: risks of teratogenicity and toxicity influencing the outcome of pregnancy are clear or a risk is strongly suspected in animal experiments and no epidemiological study has excluded the risk.
– Only data from animal experiments are available. Evaluation is not possible due to a lack of information on similar drugs and experience.
[b] Definition of evaluation while breastfeeding
○ Compatible, probably compatible: probably allowable based on epidemiological data, use experience, and pharmacological characteristics.
● Human data are limited and a basis for recommendation is lacking.
× Contraindicated: risk of toxicity of the drug is clear.
– Risk assessment is not possible due to the absence of human data.

paroxysmal tachycardia can be safely performed in pregnant women.

With β blockers, care is required regarding development of intrauterine growth restriction (IUGR) and neonatal bradycardia and hypoglycemia, but the drugs are not teratogenic and may be beneficial for the maternal condition. Treatment with oral β blockers, no matter what type of β blockers, was associated with an almost two to three-fold risk of IUGR, with adjustment of maternal variables [13,14]. However, oral β blockers may improve outcomes of pregnancy complicated by long QT syndrome and Marfan syndrome [15,16]. In particular, these pregnancies have high risks of lethal arrhythmia or aortic dissection. To prevent perinatal cardiovascular events, β blockers should be used appropriately during pregnancy and postpartum.

Amiodarone contains iodine and causes abnormality in thyroid function of fetuses, but many cases are transient. Among the 69 reported cases of amiodarone use during pregnancy, 23% of all infants developed hypothyroidism and 3% developed hyperthyroidism [17]. Since the half-life is long (about 40 days), it is important to discontinue administration a few months before conception to avoid the influence of this drug on the fetus.

The circulating plasma volume markedly changes during pregnancy and through the postpartum period, which may cause changes in the drug blood level. Therefore, time-course measurements of blood levels of drugs are recommended.

Anticoagulants and antiplatelet drugs

During pregnancy, both coagulation and fibrinolysis are augmented. Women with coagulopathy or risk of blood clots have an increased risk of thrombus and embolus, such as deep vein thrombosis and pulmonary embolism, and of complications by thrombus formation-induced valve dysfunction and embolism in cases with artificial mechanical valve replacement. For pregnancy with a high risk of thromboembolism, care is required with anticoagulant and antiplatelet therapies, and a sufficient explanation should be given and consent obtained because these drugs can influence both the mother and child.

Taking warfarin during the 6–9 weeks of gestation has an increased incidence of the fetus developing a warfarin embryopathy characterized by abnormal bone formation, nasal hypoplasia and stippled epiphyses, thought to be due to inhibition of vitamin K-dependent osteocalcins that play a role in calcification during embryogenesis. Warfarin also causes hemorrhagic complications in fetuses because it passes through the placenta. Therefore, warfarin is rather contraindicated in early and late pregnancy, and heparin is recommended as anticoagulant therapy in these periods. However, the anticoagulant action of heparin is unstable compared to that of warfarin, and the maternal death rate is 1–10% in pregnant women after mechanical valve replacement, which has the highest thrombotic risk [18,19]. Thus, selection of warfarin or heparin for anticoagulant therapy in mid-pregnancy is controversial. Since maternal safety has the first priority, the use of warfarin, even throughout the pregnancy, is one of the choices which guidelines define.

The characteristics of anticoagulants and antiplatelet drugs used in pregnancy are shown in Table 3. Previously aspirin was contraindicated in the late pregnancy because of premature constriction of the fetal ductus arteriosus. However, low-dose aspirin is now known to have no effect on fetal ductus arteriosus.

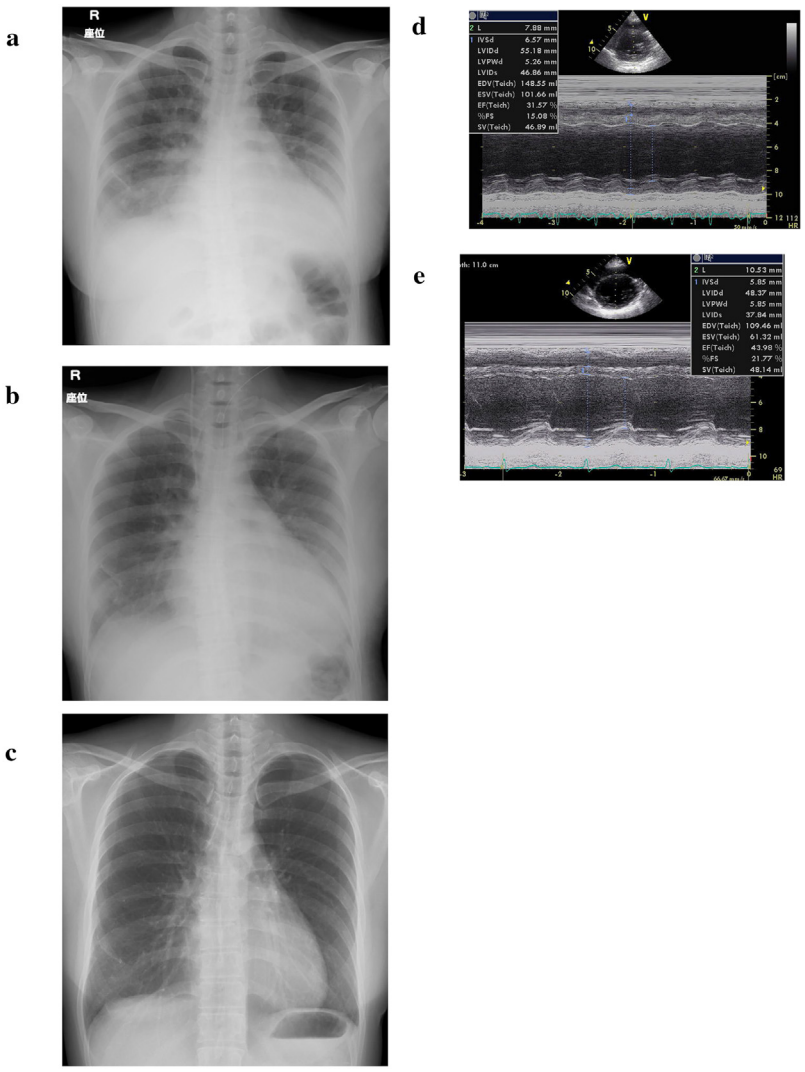

Fig. 1. Heart failure in a pregnant woman with dilated cardiomyopathy. A primipara woman with dilated cardiomyopathy, whose left ventricular ejection fraction (LVEF) was 45–50% and treated with β blocker and angiotensin receptor blocker (ARB) before pregnancy, was referred to our hospital due to heart failure at 33 weeks of gestation. After she became pregnant, both drugs were stopped. She started to complain of dyspnea on exertion at 31 weeks of gestation. She became orthopneic at 32 weeks of gestation and was diagnosed with heart failure. When she was admitted, her chest X-ray showed cardiomegaly and pleural effusion. Left ventricle end-diastolic and systolic diameters (LVDd/Ds) were 55/47 mm, and LVEF was 25–30%. Her vitals were stable, and diuretics were started on her. One week later, her pulmonary congestion was improved and Cesarean section was performed at 34 weeks of gestation. After that, β blocker and ARB were restarted. After 1 year, her LVDd/Ds were 48/37 mm, and LVEF was 38%. (a) Chest X-ray on admission, (b) chest X-ray right after Cesarean section, (c) chest X-ray one year after delivery, (d) M-mode echocardiography on admission, and (e) M-mode echocardiography one year after delivery.

Antihypertensive drugs

The incidences of complications of premature birth, IUGR, perinatal death, and superimposed preeclampsia are high in pregnant women complicated by hypertension, compared with those with normal blood pressure. However, excess reduction of blood pressure produces a hypotensive effect that collapses the balance of uterine blood flow and causes abnormal heartbeat in the fetus. The aim of maternal blood pressure control is not improvement of the fetal outcome, but alleviation of maternal complications. Previously, methyldopa and hydralazine were used as antihypertensive drugs during pregnancy, but the hypotensive effects of these drugs are lower than those of other drugs. Ca antagonists are now considered not to cause teratogenicity in humans, and these drugs can be used during pregnancy. Table 4 shows the characteristics of the main antihypertensive drugs used in pregnancy.

Drugs for pulmonary hypertension

Pregnancy complicated by pulmonary hypertension (PH) has particularly high risks for the mother and child. Pregnancy is not recommended in patients with PH because the maternal mortality rate is high, up to 50% [20]. However, some women are diagnosed with PH for the first time during pregnancy, and the maternal mortality rate has recently tended to decrease with the appearance of new drugs for PH. Prostacyclin analog is a substance produced in the fetus and no major adverse event caused by its use during pregnancy has been reported, suggesting that its benefit for maternal PH exceeds the risk for the fetus. Teratogenicity of an endothelin receptor antagonist was observed in animal experiments and its use during pregnancy is contraindicated. Table 5 shows the characteristics of the main drugs for PH in pregnancy.

Table 2
Drugs for arrhythmia in pregnancy and lactation.

Drugs	Use in pregnant women in package insert	Evaluation of use during pregnancy[a]	Influence on outcome of pregnancy and points of management	Transfer to breast milk	Evaluation of use while breastfeeding[b]
Procainamide	Benefits administration	●		+	○
Disopyramide	Avoid to use	●	Uterine contraction reported, but unclear association	+	○
Cibenzoline	Benefits administration	●		+ (animal data)	–
Lidocaine	Benefits administration	○		+	○
Mexiletine	Benefits administration	●		+	○
Flecainide	Avoid to use	▲	Animal data suggest possible teratogenic effects, but no human data	+	○
Propafenone	Benefits administration	▲	Animal data suggest possible teratogenic effects, but no human data	+	○
Pilsicainide	Benefits administration	●–▲		+ (animal data)	–
β blocker	Benefits administration	● (1st trimester: probably safe 2nd-3rd trimester: reduced fetal and placental weights)	Association of use from 2nd trimester with fetal and placental weights. Need for care for drugs without ISA. In use immediately before delivery, pay attention to appearance of β blocker action (hypotension, bradycardia and hypoglycemia) in newborn.	+	○–● (other agents may be preferred while nursing a preterm infant)
Amiodarone	Avoid to use as much as possible	▲	Fetal thyroid function may be affected because drug contains iodine.	+	× (There is a risk for abnormal thyroid function of infants due to the long half-life.)
Sotalol	Avoid to use as much as possible	● (1st trimester: probably safe 2nd–3rd trimester: reduced fetal and placental weights)	May have a risk similar to that of a β blocker	+	●
Verapamil	Avoid to use	○–●	Intravenous use is associated with a greater risk of hypotension and subsequent fetal hypoperfusion	+	○
Diltiazem	Avoid to use	●	Animal data suggest possible teratogenic effects, but no human data	+	○
Adenosine	Avoid to use	○		ND	○
Digoxin	Benefits administration	○		+	○

ND, no data.
Benefits administration: use during pregnancy only if the potential benefit outweighs the potential risk to the fetus.
[a] Definition of evaluation during pregnancy
○ Compatible: safety suggested in an epidemiological study.
● Suggest low risk: human data are limited, but the drug is considered safe based on similar drugs and experience.
▲ Suggest moderate to high risk: risk cannot be ruled out because human data are absent or limited and experience is insufficient.
× Contraindicated: risks of teratogenicity and toxicity influencing the outcome of pregnancy are clear or a risk is strongly suspected in animal experiments and no epidemiological study has excluded the risk.
– Only data from animal experiments are available. Evaluation is not possible due to a lack of information on similar drugs and experience.
[b] Definition of evaluation while breastfeeding
○ Compatible, probably compatible: probably allowable based on epidemiological data, use experience, and pharmacological characteristics.
● Human data are limited and a basis for recommendation is lacking.
× Contraindicated: risk of toxicity of the drug is clear.
– Risk assessment is not possible due to the absence of human data.

Drugs used in obstetrics and influence on circulatory dynamics

Ovulatory drugs: with advances in reproductive medicine, pregnancy acquired by infertility treatment has increased. Ovulatory drugs are used in many cases to improve ovarian failure and the rates of fertilization by artificial insemination and in vitro fertilization, but attention should be paid to complications of thrombosis and ovarian hyperstimulation syndrome (OHSS). Ovulatory drugs are seldom recommended for women with a high-risk-pregnancy, because the probability of multiple pregnancy increases. An oral drug, clomiphene citrate, promotes secretion of luteinizing hormone-releasing hormone in the diencephalon, which results in secretion of follicle-stimulating hormone from the pituitary and induces ovulation. This drug has a weak estrogen effect and complication with thrombosis in women with a thrombotic predisposition may occur. Injection of a hMG (pituitary gonadotropin) preparation induces ovulation by directly stimulating the ovary, so that the pregnancy rate is high, but the complication rates of OHSS and multiple conceptions are also high.

Uterine contraction inhibitors: the most widely used uterine contraction inhibitor in Japan is a β receptor stimulant, ritodrine hydrochloride. The effect of this drug for prevention of TPTL is the strongest among drugs currently available in Japan, but it is not recommended for patients with circulatory diseases because it increases the maternal heart rate and may induce arrhythmia and heart failure. In Europe and the USA, ritodrine hydrochloride is not used for the prevention of TPTL because of its high risk for maternal cardiovascular complications. Magnesium sulfate is a uterine contraction inhibitor that can be used in pregnant women with heart disease, but its preventive effect on TPTL has not been sufficiently established.

Uterine contraction promoters: uterine contraction promoters are used for labor induction and uterine inertia. Oxytocin and prostaglandin are mainly used because of their safety and efficacy. Oxytocin sensitivity varies depending on the gestational age, and individual differences are also large. When the duration of administration exceeds 8–10 h, sensitivity decreases and effective labor cannot be induced in many cases, even if the dose is increased. A cardiotocometer is used during oxytocia, and observation of the mother and fetus by a physician or midwife is essential. Hemorrhage from the delivering uterus does not stop

Table 3
Anticoagulants and antiplatelet drugs in pregnancy and lactation.

Drugs	Use in pregnant women in package insert	Evaluation of use during pregnancy[a]	Influence on outcome of pregnancy and points of management	Transfer to breast milk	Evaluation of use while breastfeeding[b]
Warfarin	Avoid to use	× (1st trimester)	1st trimester: warfarin embryopathy 2nd–3rd trimester: fetal hemorrhagic complications	+	○
Heparin	Benefits administration	○	Long-term therapy may be associated with maternal osteopenia.	–	○
Aspirin	Benefits administration until 12 weeks before delivery	○	Low-dose aspirin is safe.	+	○ (low-dose)
Fondaparinux	Benefits administration	–	Placental transfer of this drug is small (maximum 10%)	+ (animal data)	–
Rivaroxaban	Avoid to use	–	Animal data suggest possible teratogenic effects, but no human data	+ (animal data)	–
Dabigatran	Benefits administration	–	Placental transfer	+ (animal data)	–

Benefits administration: use during pregnancy only if the potential benefit outweighs the potential risk to the fetus.
[a] Definition of evaluation during pregnancy
○ Compatible: safety suggested in an epidemiological study.
● Suggest low risk: human data are limited, but the drug is considered safe based on similar drugs and experience.
▲ Suggest moderate to high risk: risk cannot be ruled out because human data are absent or limited and experience is insufficient.
× Contraindicated: risks of teratogenicity and toxicity influencing the outcome of pregnancy are clear or a risk is strongly suspected in animal experiments and no epidemiological study has excluded the risk.
– Only data from animal experiments are available. Evaluation is not possible due to a lack of information on similar drugs and experience.
[b] Definition of evaluation while breastfeeding
○ Compatible, probably compatible: Probably allowable based on epidemiological data, use experience, and pharmacological characteristics.
● Human data are limited and a basis for recommendation is lacking.
× Contraindicated: risk of toxicity of the drug is clear.
– Risk assessment is not possible due to the absence of human data.

Table 4
Antihypertensive drugs in pregnancy and lactation.

Drugs	Use in pregnant women in package insert	Evaluation of use during pregnancy[a]	Influence on outcome of pregnancy and points of management	Transfer to breast milk	Evaluation of use while breastfeeding[b]
Methyldopa	Benefits administration	○		+	○
Hydralazine	Benefits administration	○	Thrombocytopenia in neonates	+	○
Nifedipine	Benefits administration after 20 weeks of gestation	○	No teratogenic effect in human data	+	○
Nicardipine	Benefits administration	●		+	○
Amlodipine	Avoid to use	●		+	○
Isosorbide dinitrate	Benefits administration	●		+ (animal data)	–
Nitroglycerin	Benefits administration	●		+	○

ND, no data; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
Benefits administration: use during pregnancy only if the potential benefit outweighs the potential risk to the fetus.
[a] Definition of evaluation during pregnancy
○ Compatible: safety suggested in an epidemiological study.
● Suggest low risk: human data are limited, but the drug is considered safe based on similar drugs and experience.
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[b] Definition of evaluation while breastfeeding
○ Compatible, probably compatible: probably allowable based on epidemiological data, use experience, and pharmacological characteristics.
● Human data are limited and a basis for recommendation is lacking.
× Contraindicated: risk of toxicity of the drug is clear.
– Risk assessment is not possible due to the absence of human data.

through the general mechanism of hemostasis, such as hemostasis by platelets, but is stopped by mechanical exclusion by uterine contraction, for which rapid uterine contraction after delivery is essential. An increase in blood loss due to insufficient uterine contraction is termed atonic hemorrhage. Oxytocin and ergometrine are used to treat postpartum uterine atony, but rapid intravenous injection of oxytocin decreases blood pressure and increases heart rate. Thus, in pregnancy with cardiovascular disease, slow administration is recommended. Ergometrine has vasospastic action and is contraindicated for patients with coronary spastic angina.

Drugs used in the lactation period

In addition to passive diffusion, drugs can transfer to breast milk through active transport by membrane proteins with drug transport function present on the mammary epithelium. Drugs with low blood protein binding, basic drugs, and lipophilic (hydrophobic) drugs have increased transfer to breast milk through passive diffusion. However, since many drugs only slightly transfer to breast milk, the neonatal blood drug level during breastfeeding is normally far lower than the therapeutic range. Drugs for cardiovascular disease that are probably inappropriate for use during lactation include amiodarone [21]. Ca

Table 5
Drugs for pulmonary hypertension in pregnancy and lactation.

Drugs	Use in pregnant women in package insert	Evaluation of use during pregnancy[a]	Influence on outcome of pregnancy and points of management	Transfer to breast milk	Evaluation of use while breastfeeding[b]
Beraprost	Avoid to use	●		+ (animal data)	○
Epoprostenol	Benefits administration	●		+ (animal data)	○
Iloprost	Benefits administration	●		+ (animal data)	○
Selexipag	Benefits administration	–		+ (animal data)	–
Bosentan	Avoid to use	×	Animal data suggest possible teratogenic effects, but no human data	–	–
Sildenafil	Benefits administration	●		+	○

Benefits administration: use during pregnancy only if the potential benefit outweighs the potential risk to the fetus.
[a] Definition of evaluation during pregnancy
○ Compatible: safety suggested in an epidemiological study.
● Suggest low risk: human data are limited, but the drug is considered safe based on similar drugs and experience.
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× Contraindicated: risks of teratogenicity and toxicity influencing the outcome of pregnancy are clear or a risk is strongly suspected in animal experiments and no epidemiological study has excluded the risk.
– Only data from animal experiments are available. Evaluation is not possible due to a lack of information on similar drugs and experience.
[b] Definition of evaluation while breastfeeding
○ Compatible, probably compatible: probably allowable based on epidemiological data, use experience, and pharmacological characteristics.
● Human data are limited and a basis for recommendation is lacking.
× Contraindicated: risk of toxicity of the drug is clear.
– Risk assessment is not possible due to the absence of human data.

antagonists, β blockers, and ACE inhibitors are included as antihypertensive drugs that can be used during breastfeeding. The burden of child care, including breastfeeding, may also aggravate heart failure after delivery, and appropriate instructions on breastfeeding are necessary for women with a high-risk pregnancy. In long QT syndrome, the risk of arrhythmia is highest after delivery. For high-risk cases with a history of syncope or a familial medical history, use of a β blocker is required.

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None.

Conflict of interest

None.

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