

REVIEW ARTICLE

Cardiovascular Diseases in Pregnancy

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SUMMARY

Background: Cardiovascular diseases arise during 0.2% to 4% of all pregnancies in the industrialized world. In Germany, this type of complication, which is sometimes lethal, affects approximately 30 000 pregnant women per year.

Methods: We performed a simple literature search in the NCBI databases for publications that appeared from 2008 to 2010 and that contained the search terms “pregnancy” and one of the following: “valvular disease,” “endocarditis,” “coronary heart disease,” “cardiomyopathy,” “hypertension,” “anticoagulation.” We also took consideration of the relevant international medical society guidelines and of the new database of the *Pharmakovigilanz- und Beratungszentrum für Embryonaltoxikologie* in Berlin (Embryotox).

Results: There is a rising incidence, not only of hypertension during pregnancy, but also of valvular heart disease during pregnancy. Severe valvular stenosis, particularly mitral stenosis, raises the risk of pulmonary edema and should be treated before pregnancy, by valvuloplasty or surgically. Women with high-grade valvular insufficiency and restricted left-ventricular function are at risk of heart failure. For women with mechanical heart valves, the type of anticoagulation during pregnancy must be discussed on an individual basis. Coumarin derivatives are associated with an elevated risk of hemorrhage as well as coumarin embryopathy; recent studies have shown that the latter risk is low and dose-dependent. Spontaneous dissection of the coronary arteries is best treated by catheter intervention with the implantation of a bare metal stent.

Conclusion: Women of child-bearing age who are at risk for, or already have, cardiovascular disease should receive early counseling and treatment, not just from their family physician, but from an interdisciplinary team composed of gynecologists, cardiologists, and, if necessary, cardiac surgeons.

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Cardiovascular diseases arise during 0.2% to 4% of all pregnancies in the industrialized world. In Germany this type of complication, which is sometimes life-threatening, affects almost 30 000 pregnant women per year. The number of fetuses and neonates harmed by complications during pregnancy, labor, and delivery has not changed significantly in the last eight years (*Figure*). Approximately 6000 fetuses and neonates are affected each year.

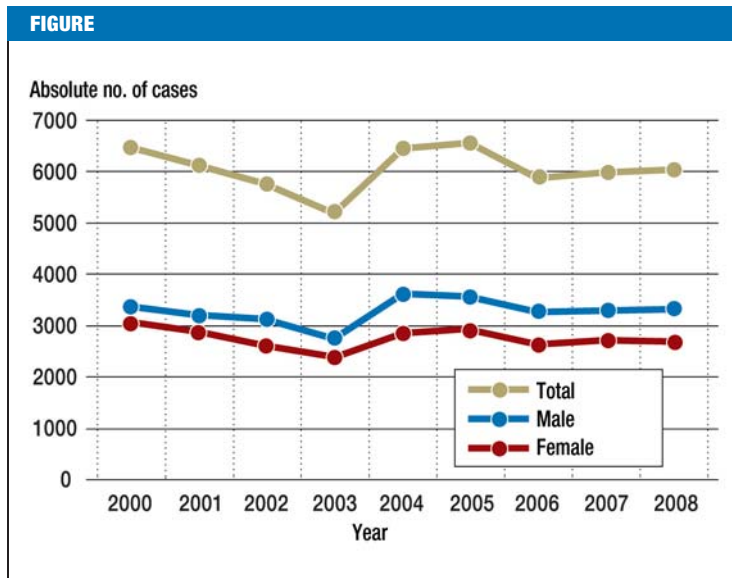
Hypertensive disorders during pregnancy are one of the commonest causes of morbidity and mortality in mothers and babies in the industrialized world. Early identification of risk factors and Doppler ultrasound scans of the uterine artery during the first and second trimesters as a predictor of preeclampsia contribute to improved care for pregnant women (1).

The proportion of women of child-bearing age with congenital heart defects, surgically treated or otherwise, has increased substantially in recent decades due to improved surgical, anesthesiological, and cardiological care. As a result, congenital heart defects currently account for approximately 30% to 50% of all cardiac diseases during pregnancy (e1). The current figure for Germany is 120 000 patients, with an annual increase of around 5000 (2). In non-industrialized countries, 90% of all heart disorders in women of child-bearing age are of rheumatic origin. Worldwide, mitral stenosis is the most common valve defect responsible for maternal deaths with cardiac causes. It requires therapeutic intervention before or during pregnancy. Acquired heart valve defects account for 15% of cardiac complications in pregnant women in the industrialized world (3).

Cardiomyopathy, arrhythmia and coronary heart disease are considerably rarer diseases but can also lead to complications during pregnancy. There are new therapeutic approaches for peripartum cardiomyopathy (PPCM). Specific treatment involving bromocriptine (to inhibit prolactin byproducts) has shown positive results so far in pilot studies. Bromocriptine combined with an anticoagulant, due to the increased risk of thrombosis, is therefore currently being investigated in a prospective study in the treatment of peripartum cardiomyopathy (4).

This review article concentrates on heart valve disorders, endocarditis, and coronary heart disease. Anticoagulants are often indicated for these clinical

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Hospital diagnosis data for ICD-10: P00-P04, 2000–2008: approximately 6000 fetuses per year harmed as a result of complications during pregnancy, labor, and delivery, out of a total number of 349 862 male and 332 652 female live births in Germany in 2008. Source: Federal Health Reporting, Federal Statistical Office, Robert Koch Institute, Berlin

conditions, to minimize the risks to mother and infant. Hypertension, arrhythmia, and peripartum cardiomyopathy have already been explored in detail in earlier *Deutsches Ärzteblatt* articles (1, 5) (e2).

For almost all medical issues during pregnancy, there are very few prospective randomized trials. Treatment decisions are essentially based on observational studies and case descriptions. Many recommendations are based on evidence of only grade C, expert opinion.

Methods

We gathered data from a simple literature search in the databases of the National Center for Biotechnology Information (NCBI), using the search terms “pregnancy” and one of the following: “valvular disease,” “endocarditis,” “coronary heart disease,” “cardiomyopathy,” “hypertension,” “anticoagulation.” 196 German- and English-language publications dating from between 2008 and 2010 were analyzed, in addition to the guidelines of medical associations on new aspects of diagnosis and treatment (3, 6, 7). We also consulted the Embryotox database (www.embryotox.de, in German) of the *Pharmakovigilanz- und Beratungszentrum für Embryonaltoxikologie* in Berlin for pharmacological data.

Cardiovascular adaptation, diagnosis, and risk stratification

Physiological changes during pregnancy put a strain on the heart and can mimic heart disorders. The heart rate rises by between 10 and 30 beats per minute, and cardiac output increases by 30% to 50% by the 32nd week of pregnancy. Vasodilation as well as reversible enlargement of the heart of up to 30% develop (e3).

Systolic blood pressure falls during the first half of pregnancy and returns to previous levels towards the end of pregnancy. During labor and vaginal delivery, maternal oxygen consumption rises up to threefold. Blood pressure spikes of up to 200 mm Hg are possible during the stage of expulsion. This leads to increased blood clotting and an increase in blood serum lipids (8). ECG alterations such as negative T waves can also occur with no pathological correlate. As CK and CK-MB are also expressed in the uterus and the placenta, their diagnostic value is limited. Cardiac troponins can be used to diagnose ischemia (9).

In addition to basic examinations, exercise ECG, echocardiography, and stress echocardiography without the use medications are extremely important in diagnosing ischemia. Stress of up to 70% of maximum heart rate is recommended (3). Procedures involving nuclear medicine are contraindicated; MRI scans should be used instead. Radiological guidelines for MRI use require risk/benefit analysis during the first trimester, as residual risks to the fetus have not yet been completely ruled out (6). Cardiac catheter examinations are only justified if absolutely essential. If they are performed, access via the arteria radialis is preferred.

One tool to assess the risks of pregnancy-related diseases in the mother is the Siu risk score (10). Contraindications to pregnancy according to the score are stated in the *Box* (3).

Delivery

Vaginal delivery is always recommended when the patient is hemodynamically stable at the end of pregnancy. A natural birth is possible even when there is manifest coronary heart disease. Peridural anesthesia and assisted vaginal delivery should be used to minimize the duration of labor. The use of drugs to induce labor should be avoided whenever possible.

Patients with advanced heart failure (NYHA class III/IV) and hemodynamic instability, particularly if there is severe aortic stenosis and in patients with Marfan syndrome, should undergo primary abdominal Cesarean section, in the 38th week of pregnancy if possible. When selecting anesthesia, a decrease in peripheral vascular resistance should be avoided if there are stenotic heart defects.

Acquired heart valve defects

In Germany, 1798 women aged between 15 and 45 years were treated in a hospital for mitral and/or aortic defects in 2008 (11). Due to increasing numbers in recent decades of valvular heart defects with hemodynamic effects, surgically treated or otherwise, problems during pregnancy can be expected to occur more often. Acquired heart valve defects are responsible for 15% of cardiac complications in pregnant women in the industrialized world.

Table 1 provides an overview of the complications typical of each defect. Patients with high-grade stenotic malformations are particularly at risk due to hemodynamic alterations during pregnancy and childbirth.

During labor, the rapid rise in cardiac output, heart rate, and blood pressure may lead to pulmonary edema, particularly if the mother suffers from mitral stenosis. In patients with obstruction of the left ventricle, the main risks are of diastolic heart failure and arrhythmia (12). In patients with valve insufficiency and restricted left ventricular function, this can lead to heart failure. Postpartum, the risk of this is higher, due to the increased venous return flow.

Patients with heart valve defects should receive detailed cardiological counseling on the risks of pregnancy before becoming pregnant. An interdisciplinary treatment plan should be drawn up in case they become pregnant.

Mitral stenosis (MS)

Asymptomatic women with valve aperture area $>1.5 \text{ cm}^2$ usually tolerate pregnancy well. If heart rate or venous return flow increases postpartum, beta-1 selective beta-blockers and diuretics can be administered, initially at low doses (3).

In patients with moderate and severe MS (valve aperture area $<1.5 \text{ cm}^2$), balloon valvuloplasty should be performed before pregnancy, regardless of clinical symptoms, as there is a risk of pulmonary edema, often accompanied by tachyarrhythmia (3). Balloon valvuloplasty is the treatment of choice and even during pregnancy can be performed with low complication rates. Maternal and fetal mortality following valvuloplasty is $<1\%$ and morbidity is also low, at 2% to 4%. The most common complication is mitral insufficiency (e4).

If there is severe calcification of the valve, a closed commissurotomy can be considered. Maternal mortality is $<2\%$, and fetal mortality between 2% and 8%. With open commissurotomy or valve replacement, fetal mortality is between 10% and 30%.

Biological prostheses are favored for valve replacements, although they do have the following disadvantages:

- High degeneration rate: between 10% and 30%
- Reoperation rates between 30% and 50% after 10 years, with
- Perioperative mortality between 3% and 10% (13).

Artificial prostheses require anticoagulants even during pregnancy. This requires intensive risk analysis, due to the associated problems of coumarin embryopathy and hemorrhaging complications (14).

Aortic stenosis

In the industrialized world, most aortic valve stenoses in women of child-bearing age are congenital bicuspid aortic valves. In non-industrialized countries, rheumatic origin is the most common.

While patients with mild and moderate aortic stenosis often tolerate pregnancy with no complications, severe aortic stenosis (valve aperture area $<1.0 \text{ cm}^2$ or $<0.6 \text{ cm}^2/\text{m}^2$ body surface; average Doppler ultrasound pressure gradient $>50 \text{ mm Hg}$) is associated with a significantly increased risk to the fetus and risk to the

BOX

Cardiovascular diseases that make pregnancy unadvisable*

- High-grade pulmonary hypertension of any origin ($\geq 50\%$ of systemic pressure)
- Severe left or right ventricular dysfunction (LV ejection fraction $<40\%$)
- Patients with severe heart failure (NYHA class III/IV)
- Severe left heart obstruction (aortic stenosis with average pressure gradient $>50 \text{ mm Hg}$ according to Doppler ultrasound, high-grade [recurrent] aortic isthmus stenosis)
- Severe mitral stenosis (average pressure gradient $>10 \text{ mm Hg}$, valve aperture area $<1 \text{ cm}^2$)
- Marfan syndrome with ectasia of the aorta ascendens ($\geq 45 \text{ mm}$)
- Cyanotic heart disease (especially with oxygen saturation $<80\%$)

*modified according to (3)

mother of heart failure and cardiac arrhythmias (12). Symptomatic patients with severe aortic stenosis and asymptomatic women with restricted left ventricular function or a pathological stress ECG should be advised against becoming pregnant and should ideally undergo valvuloplasty or surgery before a planned pregnancy (3). If valvuloplasty cannot be performed, heart valve replacement should be considered. A Ross operation (replacement of the aortic valve using an autologous pulmonary valve and implantation of a homograft or biological prosthesis in the pulmonary position) has the advantage, for women who wish to have children, that no anticoagulants are required even if the patient later becomes pregnant. However, because of the high reoperation risk in adults this is a controversial procedure (15).

Cardiologists should closely monitor asymptomatic women with severe aortic stenosis not diagnosed until pregnancy, normal left ventricular function, and a normal stress ECG as part of their care. Symptomatic treatment involves diuretics. In the event of heart failure, beta-1 selective beta-blockers are also used, and reduced physical activity is recommended. For patients who do not respond to drug treatment and for whom early delivery is impossible, a valvuloplasty or valve surgery must be performed during pregnancy (3).

Aortic insufficiency and mitral insufficiency

Due to their reduced peripheral vascular resistance, patients with only moderate to severe valve insufficiency tolerate pregnancy well provided their left ventricular function is normal. Patients whose main symptom is shortness of breath respond well to restricted salt

TABLE 1

Maternal and neonatal complications in acquired valve defects*

Defect	Severity	NYHA class	Maternal complications	Neonatal complications	Recommendations	Recommendation of evidence
Mitral insufficiency						
	Mild	I-II	Rare: CA	None	Monitoring; med. only for symptomatic CA	I-C
	Moderate	I-II	Slightly increased: CA, rare: HF	None	Med. for CA	IIa-C
	Severe	III-IV	Significantly increased: CA, HF, PE, EC	Increased: 1, 2, 3	Pregnancy before surgery contraindicated	I-C
Mitral stenosis						
	Mild	I	Rare: CA	None	Monitoring; med. only for symptomatic CA, beta-blockers	I-C
	Moderate	II	Increased: CA, TE, PE, EC	Increased: 1, 2, 3	For atrial fibrillation: anticoagulants, beta-blockers, digitalis, verapamil to control heart rate, valvuloplasty ideally before pregnancy, and if symptomatic also during pregnancy	IIa-C
	Severe	II-IV	Greatly increased: CA, PE, EC	Increased: 1, 2, 3	No pregnancy before valvuloplasty; in pregnant women with symptoms valvuloplasty can be performed	I-C
Aortic insufficiency						
	Mild	I-II	None	None	Monitoring	I-C
	Moderate	I-II	Rare: CA, HF	Rare: 1, 2	Med. for CA and HF	IIa-C
	Severe	III-IV	Increased: CA, HF, EC	Increased: 1, 2	No pregnancy before surgery	I-C
Aortic stenosis						
	Mild	I	Rare: CA	None	Monitoring; med. only for symptomatic CA	I-C
	Moderate	II	Increased: HF, CA	Increased: 1, 2, 3	Med. for CA and HF	IIa-C
	Severe	III-IV	Greatly increased: HF, CA, sudden cardiac death	Increased: 1, 2, 3	No pregnancy before intervention (valvuloplasty/surgery); bed rest during 3 rd trimester of pregnancy; C section	I-C

EC: endocarditis; HF: heart failure; PE: pulmonary edema; med: medication; CA: cardiac arrhythmias, TE: thromboembolism; Neonatal complications: 1 = intrauterine growth retardation: 2 = low birth weight: 3 = stillbirth
*modified according to (3)

intake, diuretics and digitalis. Precautionary use of nifedipine or hydralazine is possible if patients exhibit hypertension. Patients with NYHA class III/IV or restricted left ventricular function are at significantly higher risk and should undergo heart surgery, preferably reconstructive, before pregnancy.

Mechanical heart valve prostheses and anticoagulants

Hemodynamically, patients with mechanical heart valves tolerate pregnancy well provided their left ventricular function is not restricted and they do not suffer from pulmonary hypertension.

The necessary oral anticoagulants are associated with an increased risk of hemorrhage and a risk of coumarin embryopathy; recent studies have shown that the

latter risk is low (16, 17) and dose-dependent (18, 19). No embryopathy is observed with warfarin doses <5 mg, equivalent to <3 mg phenprocoumon. At higher doses, the rate was 8% (18, 19).

Continued oral administration of anticoagulants until the 36th week of pregnancy and a subsequent switch to unfractionated heparin until delivery is the safest treatment for the mother (14). Anticoagulation using low-molecular weight heparin in the first trimester is only justified when regular monitoring of anti-factor Xa activity (1.0–1.2 U/L) is guaranteed and high doses of phenprocoumon are required (3, 7). If anticoagulation is inadequate during pregnancy, the mother is at high risk of valve thrombosis and thromboembolism. An overview of current anticoagulation medication is provided in *Table 2* (14).

TABLE 2

Anticoagulants during pregnancy

Drug	Teratogenic in humans	Fetotoxicity	Relative dose during lactation	Recommendation
Heparin, unfractionated	No	No	Does not pass into BM	Drug of choice except with MHVR
Low-molecular weight heparin	No	No	Does not pass into BM	Drug of choice; not to be used with MHVR (no approval)
Phenprocoumon	Coumarin embryopathy	CNS hemorrhage	Max. 10%, no abnormal findings in breastfed children	Stop/replace no more than 8 weeks after LMP; except with MHVR
Low-dose ASA	No	No	No abnormal findings in breastfed children	Can be used
Clopidogrel	No	No	Insufficient data available	Second-line drug
Ticlopidine	Insufficient data available	Insufficient data available	Insufficient data available	Refrain from using, as insufficient data available
Danaparoid	Well tolerated so far	Well tolerated so far	No anti-Xa activity in BM	Alternative to heparins, e.g. with HIT
Desirudin	No	No	Insufficient data available	Second-line drug
Argatroban	Insufficient data available	Tolerated (isolated cases)	Insufficient data available	Refrain from using, as insufficient data available
Fondaparinux	Insufficient data available	Tolerated (isolated cases)	Insufficient data available	Second-line drug

BM: breastmilk; MHVR: mechanical heart valve replacement; LMP: last menstrual period; ASA, acetylsalicylic acid; HIT, heparin-induced thrombocytopenia

Endocarditis

Endocarditis rarely occurs during pregnancy: its incidence is approximately 0.006% (e5) and 0.5% when there is known history of heart disease (e6). Maternal mortality is 33%, and fetal mortality 29% (7). Common life-threatening complications are severe valve insufficiency with subsequent heart failure or an embolic event. In a pregnant woman with fever of unknown origin and heart murmur, differential diagnosis of endocarditis should be considered.

Many antibiotics have not been sufficiently researched in pregnant women. However, most are not suspected of causing prenatal toxicity. Penicillins, cephalosporins, and macrolides are preferred. Second-line drugs include cotrimoxazole and, until the 15th week of pregnancy, doxycycline, in addition to the gyrase inhibitors ciprofloxacin and norfloxacin (e7). Due to their ototoxicity, systemic treatment with aminoglycosides should only be used when absolutely essential.

Heart valve replacement during pregnancy is associated with increased maternal mortality. Its rates of prenatal and perinatal child mortality are 25% to 30% (20). However, for severe, acute, treatment-resistant valve insufficiency, obstruction of a duct or shunt, or treatment-resistant staphylococcal endocarditis, risk benefit analysis may favor heart surgery.

Due to a paradigm shift regarding prophylactic antibiotic treatment for endocarditis, it is now indicated only for high-risk patients, similar to the indications for non-pregnant patients. Prophylactic antibiotic treatment should be administered to women who undergo

dental surgery during pregnancy following endocarditis and following heart valve replacement, for example. Prophylaxis during delivery is not recommended according to the guidelines of the European Society of Cardiology (7).

For antibiotic prophylaxis of rheumatic fever, the recommendations are the same as for non-pregnant patients: continuous prophylaxis for at least five years or until the age of 21 years. This affects mainly young women who are not from Western Europe or North America.

Coronary heart disease and myocardial infarction

According to data of the MONICA/KORA myocardial infarction registry (Augsburg) from 1987 and 2007, the number of men and women in Germany dying of myocardial infarction is falling. Heart attacks are becoming more common among young women, however (21).

Nevertheless, clinical manifestations of coronary heart disease occur only rarely in pregnant women. As a result, very few cases of myocardial infarction during pregnancy or childbirth have been reported (22). In these cases the reported mortality rates were high, at 20% to 37% for the mother and 17% for the infant (e8, e9).

Risk factors and pathophysiology

The most common risk factors among women are nicotine consumption and diabetes mellitus (e10). Others include the following:

- Hyperlipidemia
- Arterial hypertension (particularly preeclampsia/eclampsia)
- Obesity
- Family history
- Hyperhomocysteinemia (3).

Alongside common plaque rupture in a coronary vessel altered due to arteriosclerosis, angina pectoris symptoms and myocardial infarction also occur in angiographically normal coronary vessels. These are due to local coronary thromboses and continuous coronary spasms (sometimes caused by bromocriptine, oxytocin and prostaglandin). One particular form of coronary heart disease not caused by arteriosclerosis is spontaneous dissection of the coronary arteries, which occurs mainly in the third trimester and up to three months postpartum (23). Pathophysiologically, there is infiltration of eosinophils into the adventitia (8). Coronary abnormalities and vasculitis can also lead to myocardial ischemia during pregnancy and childbirth (3).

Treatment

Beta-1selective beta-blockers are the drugs of choice for coronary heart disease. Nitrates can also be used in symptomatic patients. Thrombocyte aggregation inhibition using acetylsalicylic acid (ASA) as secondary prevention is controversial, due to the increased risk of hemorrhage (22). However, it should be administered following coronary intervention (PCI) with stent implantation and following myocardial infarction. There are insufficient data available on clopidogrel. ACE inhibitors are contraindicated after the first trimester. Statins should not be prescribed, as they have not yet been proved safe (24).

Management of acute coronary syndrome (ACS) and myocardial infarction require close cooperation between cardiologists and gynecologists. Coronary angiography with possible PCI is preferable to thrombolysis, particularly when spontaneous dissection of the coronary arteries is suspected. Bare stents should be used where possible. During the first trimester extremely meticulous risk/benefit analysis must be carried out, due to the potential harm to the fetus (25). No teratogenic effects of thrombolysis have been described, as thrombolytic drugs do not generally cross the placental barrier. However, there is an increased risk of hemorrhage.

Conclusion

Women of child-bearing age with known heart valve defects, evidence of heart disease, or risk factors for coronary heart disease should be treated early. In addition to their family physicians, they should also be counseled and treated by an interdisciplinary team of gynecologists, pediatric and adult cardiologists, and, if necessary, cardiac surgeons, in order to minimize maternal and fetal mortality. As individual doctors will be faced with such patients only rarely, guidelines are particularly important.

Conflict of interest statement

Dr. Kruck received fees for talks from Sanofi-Aventis, Daiichi Sankyo, Berlin-Chemie, Astra Zeneca, and Pfizer. The other authors declare that no conflict of interest exists.

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KEY MESSAGES

- Cardiovascular diseases are the most common cause of maternal death during pregnancy in the Western industrialized world. Women of child-bearing age with heart disease or cardiovascular risk factors should therefore be counseled and treated early by an interdisciplinary team of gynecologists, cardiologists, and, if necessary, cardiac surgeons.
- Patients with severe stenotic heart valve disorders should undergo catheterization or surgery before becoming pregnant.
- Oral anticoagulants must be discussed on an individual basis for mechanical heart valve replacement. They are associated with an increased risk of hemorrhage and coumarin embryopathy. Recent studies have shown the risk to be low and dose-dependent.
- Prophylaxis for endocarditis is only indicated for high-risk patients. Prophylaxis during delivery is not recommended according to the most recent guidelines of the European Society of Cardiology.
- Spontaneous dissection of the coronary arteries, which is most common in the third trimester and up to three months postpartum, should ideally be treated using catheterization and implantation of a bare stent.

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REVIEW ARTICLE

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