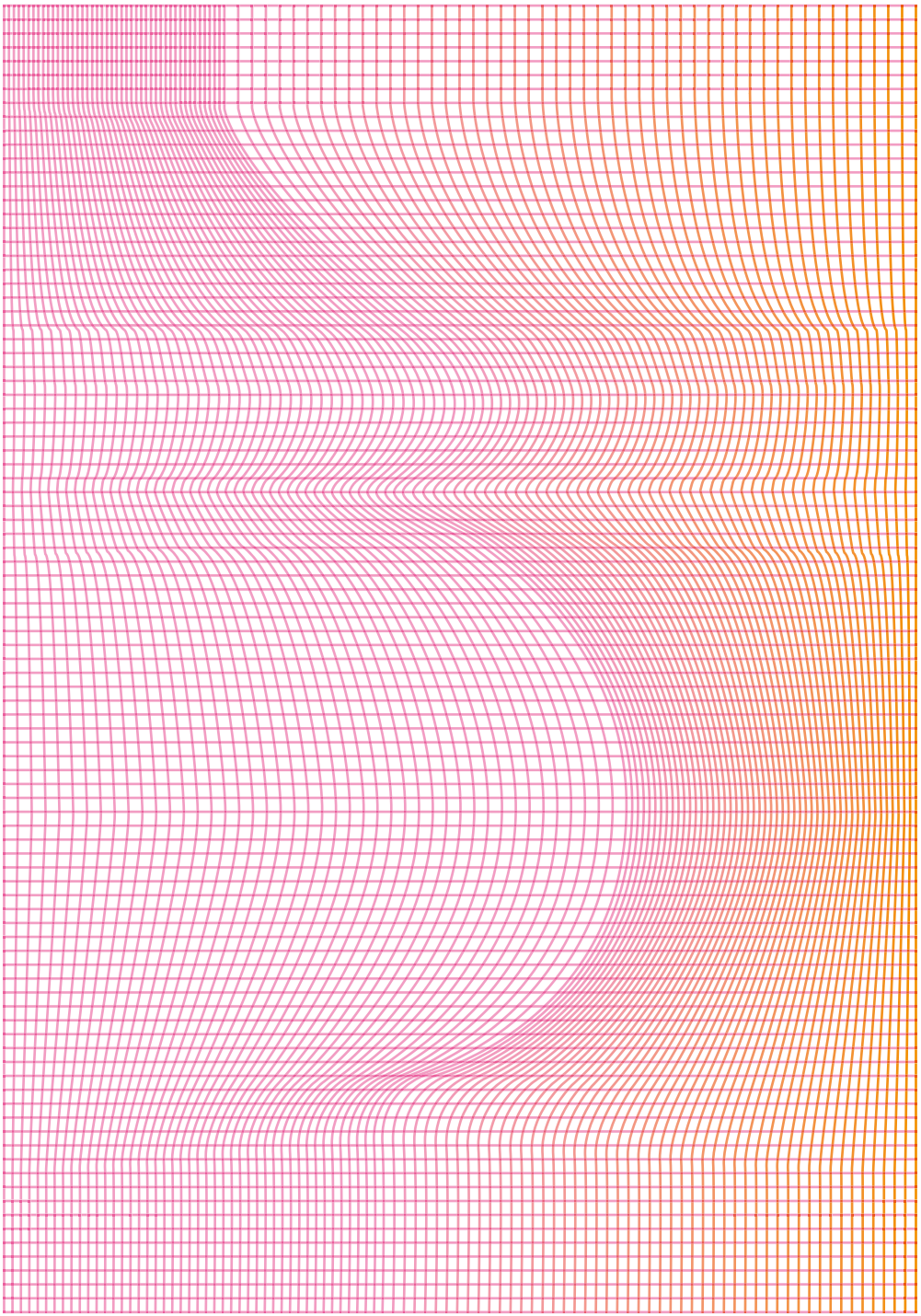

Severe maternal cardiovascular pathology and pregnancy

Heleen Lameijer

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Aan mijn ouders

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Colophon
Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged. The research described in this thesis was supported by a grant of the Dutch Heart Foundation [2009B013].

Other financial support by the Dutch Society of Emergency Physicians [Nederlandse Vereniging voor Spoedeisende Hulp Artsen, NVSHA], the Medical Centre Leeuwarden [Medisch Centrum Leeuwarden, MCL], the UMCG Cardiology fund [UMCG Cardiologiefonds] and the Foundation for Optimization of Emergency care in the North of the Netherlands [Stichting Optimalisering Spoedzorg Noord-Nederland] was applied for, granted and gratefully acknowledged.

Graphic design: www.studioanne-marijn.com
Printed by: Netzodruk, Groningen

ISBN printed version: 978-94-034-1012-8
ISBN digital version: 978-94-034-1011-1

rijksuniversiteit groningen

Severe maternal cardiovascular pathology and pregnancy

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

maandag 12 november 2018 om 11:00 uur

door

Heleen Lameijer

geboren op 17 september 1987
te Delfzijl

Promotor
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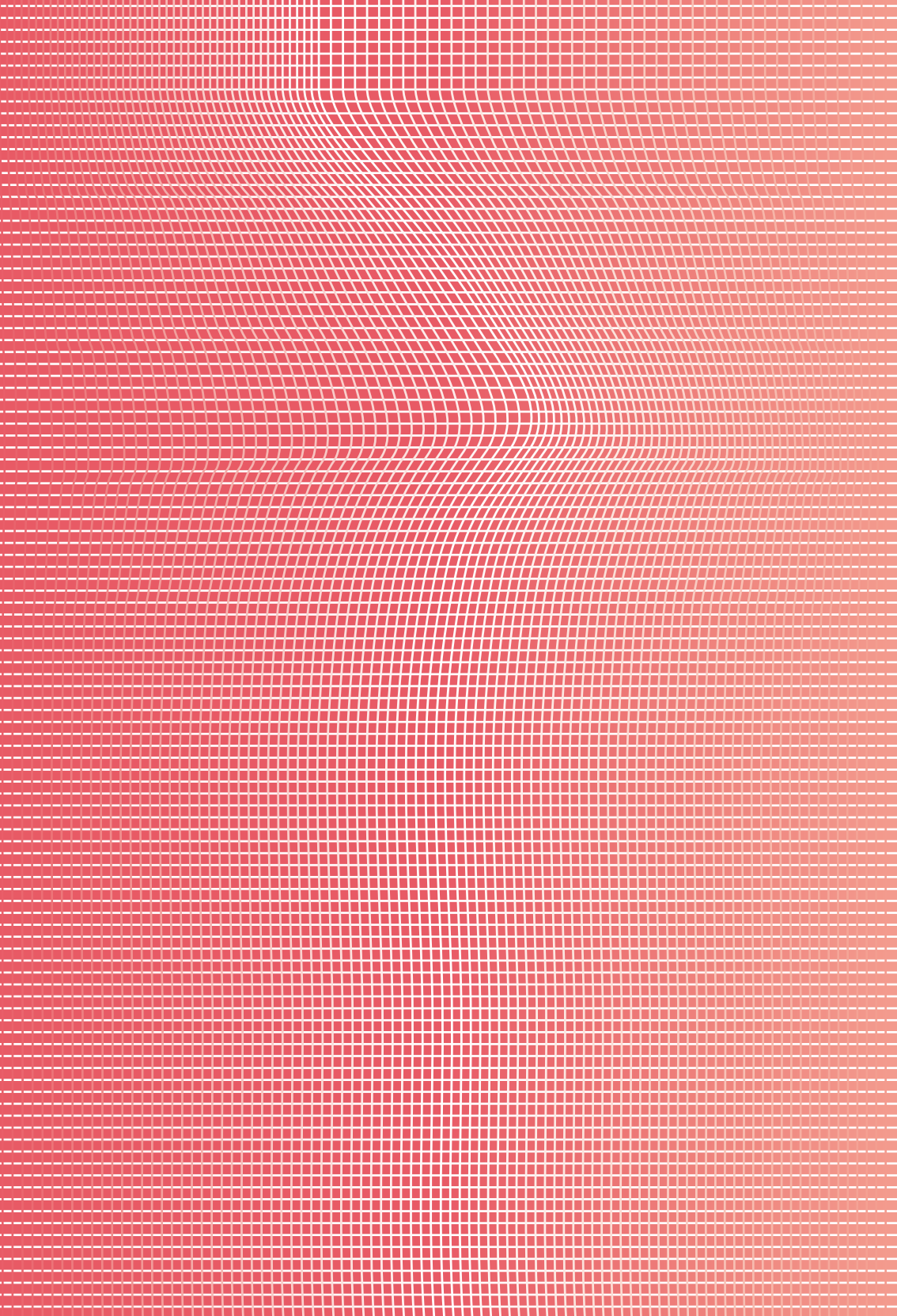

1

INTRODUCTION

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1 – 10

PREGNANCY, CARDIOVASCULAR DISEASE, AND WHY IT MATTERS

Nowadays cardiovascular diseases are the leading cause of indirect maternal mortality in European countries, including the Netherlands.[1-4] Moreover, from 1993-2005 a rise of the indirect maternal death including cardiovascular deaths was observed in the Netherlands, as well as a rise of direct maternal mortality including (unexplained) sudden deaths (of possible cardiovascular origin).[2]

In addition, cardiovascular diseases are also accountable for significant and sometimes severe maternal as well as foetal morbidity.[5-7] In the future, the incidence of cardiovascular diseases during pregnancy is expected to increase worldwide. This is due to increasing maternal age and deteriorating lifestyle choices leading to a higher incidence of obesity and diabetes mellitus, and therefore a higher incidence of risk factors for cardiovascular disease.[8] However, studies providing high quality data regarding complication risk and management of (new onset) severe cardiovascular diseases during pregnancy, including their maternal and foetal risks and thereby possible prevention of maternal and foetal mortality, is scarce.[9]

WHY IS PREGNANCY A RISK FOR WOMEN WITH KNOWN CARDIOVASCULAR DISEASE?

During pregnancy and the post-partum period cardiovascular and hemodynamic changes occur including an expansion of blood volume, lowering of systemic vascular resistance and blood pressure (due to the expansion of the low-resistance utero-placental vascular bed as with increased blood flow) and an increase in cardiac output (accomplished by increased stroke volume and increased heart rate).[10-14] Another physiological adaptation to pregnancy is the change of several coagulation factors resulting in a 20 percent reduction of prothrombin and partial thromboplastin times, called the hypercoagulable state.[15]

In women with known cardiovascular disease, the cardiovascular and hemodynamic changes occurring during pregnancy can precipitate severe complications, such as heart failure and, as stated, even death. While the majority of pregnant women with heart disease have congenital heart disease, severe morbidity and mortality rates are relatively low in these patients. Exceptions are women with uncorrected cyanotic disease, Eisenmenger syndrome, aortic diseases, severe outflow tract obstruction, failure of the systemic ventricle, and women with prosthetic valves. In pregnant women with prosthetic valves anticoagulation therapy is challenging because the hypercoagulative state of pregnancy increases the risk of thrombo-embolic complications. Furthermore, there is the risk of foetal malformations associated with the use of vitamin K

antgonists.[9 16] Women with pulmonary hypertension are currently advised against pregnancy, however, because treatment regimen in these women have been improving in recent years, pregnancy risk needs revaluation.[9] And while women with other cardiovascular disease, such as ischemic heart disease, heart valve disease or cardiomyopathy, will consider pregnancy, pregnancy risk for these women as well as their offspring is not well defined.[9]

NEW ONSET CARDIOVASCULAR DISEASES DURING PREGNANCY AND THEIR DIAGNOSIS

In previously healthy women, the cardiovascular and hemodynamic challenges of pregnancy and changes in coagulation can induce the first manifestation of cardiovascular disease, including ischemic heart disease, aortic dissection and (peripartum) cardiomyopathy. Recognition of these cardiovascular diseases can be difficult in pregnant women. One of the reasons is similarity of the symptoms with normal pregnancy discomforts, such as chest pain due to reflux disease or normal pregnancy oedema and dyspnoea due to the pressure of the gravid uterus on the lungs and vena cava. Also, because cardiovascular disease in young women is scarce and obstetricians often are relatively unfamiliar with cardiovascular diseases in pregnancy, physicians may easily miss these diagnoses. Furthermore, diagnostic testing can be challenging, for example because of pregnancy-associated physiological supra-normal d-dimer levels and because of relative contra-indication and therefore reluctance for CT scanning during pregnancy.[17 18] Even simple diagnostic tools such as an electrocardiogram can pose interpretation problems during pregnancy. For example, ST-segment changes can occur during pregnancy due to the haemodynamic changes and positional changes of the heart caused by uterine growth.[19]

TREATMENT OF CARDIOVASCULAR DISEASES DURING PREGNANCY

Certain drugs which are normally used in several cardiovascular diseases are contraindicated during pregnancy, such as angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, amiodarone and spironolactone.[20]

Antithrombotic therapy with acetylsalicylic acid is safe during pregnancy. The use of clopidogrel appears to be safe in animal models, but is discouraged because of limited experience in humans.[20] Direct oral anticoagulants (DOACs), while increasingly used, have still unknown efficacy and safety during due to exclusion of pregnant women in DOAC study protocols.[21 22] Vitamin K antagonists are associated with increased risk of pregnancy loss and with embryopathy, especially at higher dosages.[20 23] Anticoagulation with unfractionated or low-

molecular weight heparin appears to be associated with increased risk of PHV thrombosis, even when monitoring of anticoagulation effect and dose adjusting is performed according to guidelines.[24-27]

Lastly, there is still a difficulty in the choice of type of PHV as surgical treatment for heart valve disease in young women. This is both due to the issues mentioned regarding to anticoagulation management as well as issues regarding heart valve deterioration before and during pregnancy.[28 29]

THE AIM OF THIS THESIS

In this thesis we aim to evaluate the specific cardiovascular causes of maternal death and identify factors related to the cardiovascular maternal mortality in the Netherlands (Chapter 2). We further specify the pregnancy risk for mother and foetus in specific severe cardiovascular diseases with high maternal mortality including new onset and pre-existing ischemic heart disease (Chapter 3-6), valvular heart disease with PHV (Chapter 7) and pulmonary hypertension (Chapter 9). We will discuss treatment with anticoagulation medication during pregnancy in women with PHV and in women using DOACs during pregnancy (Chapter 7 and 8). Overall, we search for possibilities for improvement of pregnancy care in these women and provide recommendations in an attempt to contribute to a reduction of the increasing cardiovascular maternal mortality and morbidity.

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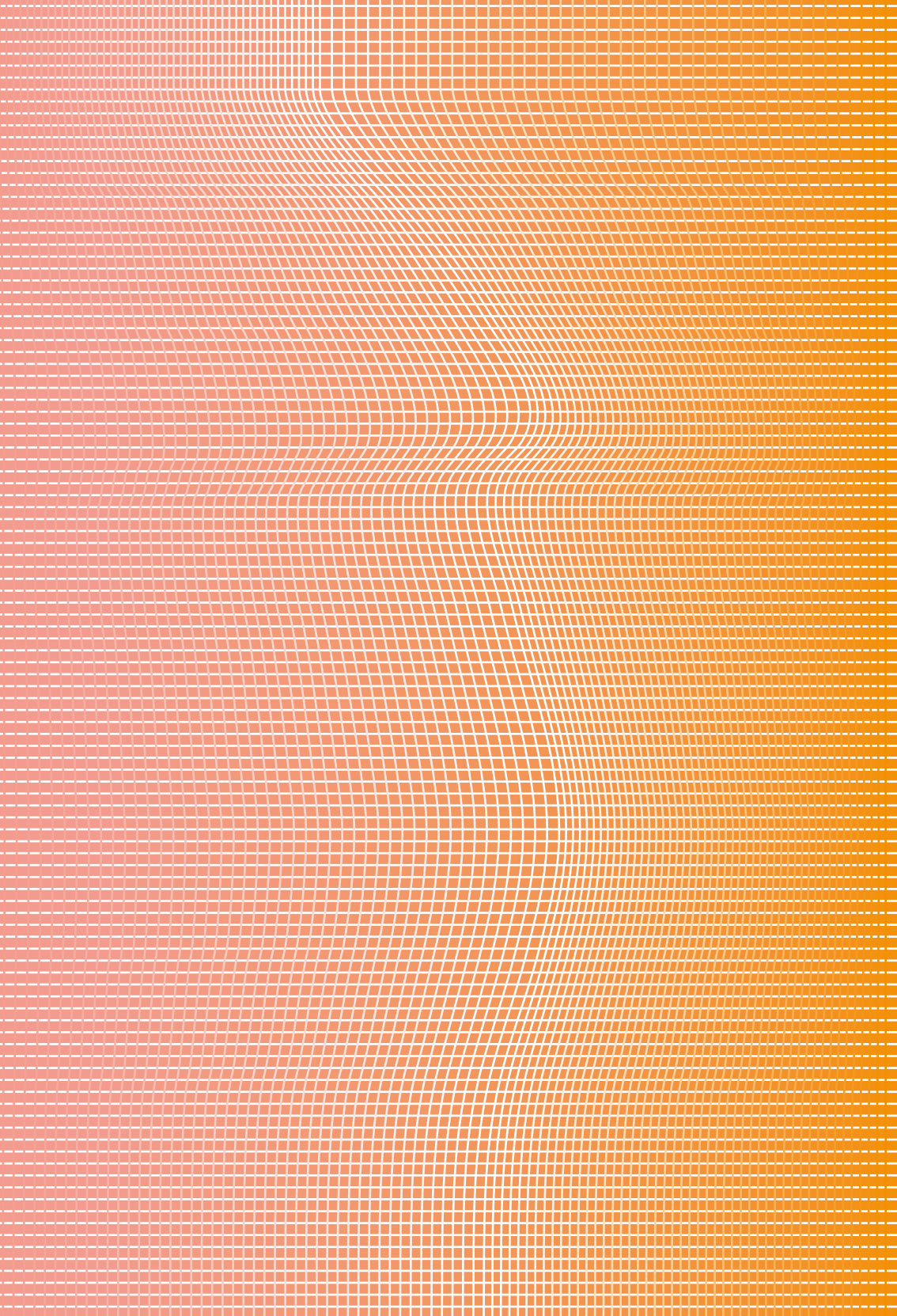

2

Maternal mortality due to cardiovascular disease in the Netherlands: a 21 years' experience

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ABSTRACT

Objective

Cardiovascular disorders are the leading cause of indirect maternal mortality in Europe. The aim of this study is to present an extensive overview concerning the specific cardiovascular causes of maternal death and identify avoidable contributing care factors related to these deaths.

Methods

We assessed all cases of cardiovascular maternal death collected by a systematic national confidential enquiry of maternal deaths published by the Dutch Maternal Mortality Committee (MMC) on behalf of the Netherlands Society of Obstetrics and Gynaecology over a 21-year period (1993-2013) in the Netherlands.

Results

There were 96 maternal cardiovascular deaths (maternal mortality rate from cardiovascular diseases 2.4/100.000 live born children). Causes were aortic dissection (n=20, 21%), ischemic heart disease (n=17, 18%), cardiomyopathies (including peripartum cardiomyopathy and myocarditis, n=20, 21%) and (unexplained) sudden death (n=27, 28%). Most deaths occurred postpartum (n=55, 55%). Care factors that may have contributed to the adverse outcome were identified in 27 cases (28%). These factors were patient-related in 40% (pregnancy against medical advice, underestimation of symptoms) and health care provider related in 60% (no recognition or delay of diagnosis, delay in referral).

Conclusion

Maternal cardiovascular mortality ratio is low in the Netherlands and the main causes of maternal cardiovascular mortality are in line with other European reports. In a minority contributing care factors that were possibly preventable were identified. Women with cardiovascular disease should be properly counselled about risks of pregnancy and symptoms of complications. Education of care providers about the incidence, presentation and diagnosis of cardiovascular disease during pregnancy is advised to further improve maternal outcome.

INTRODUCTION

Cardiovascular disorders (CVD) are the leading cause of indirect maternal mortality in European countries, including the Netherlands.[1-4] Moreover, in the Netherlands a rise of the indirect maternal death ratio (including cardiac deaths) was observed from 1993-2005.[2] Also, a rise of direct maternal mortality was observed, which includes (unexplained) sudden deaths. An ongoing national systematic confidential enquiry of maternal deaths is performed in the Netherlands by the Dutch Maternal Mortality and Morbidity Committee (MMMC) on behalf of the Netherlands Society of Obstetrics and Gynaecology. Data and conclusions are periodically (inter)nationally published. The enquiry assesses the prevalence and causes of maternal deaths and identifies contributing care factors that may be related to the adverse outcome, with the aim to further reduce mortality and morbidity in the Netherlands. On behalf of the MMMC, the aim of our study is to present an extensive overview concerning the specific cardiovascular causes of maternal death and identify factors related to the rise in cardiovascular maternal mortality in the Netherlands over a 21-year period.[2 3] Furthermore, we will address possibilities for improvement of care in these women and provide recommendations in an attempt to contribute to a reduction of cardiovascular maternal mortality.

METHODS

We used data collected by the MMMC. The members of the MMMC (eleven obstetricians and one obstetrically orientated anaesthetist working in the field of maternal medicine, both from university and non-university hospitals) are appointed by the Dutch Society of Obstetrics and Gynaecology. Maternal mortality cases were voluntarily reported to the MMMC by obstetricians and in some cases by midwives and general practitioners. A request to report every death to the MMMC during or within 1 year after pregnancy in the study period was submitted to all 98 obstetric departments in the Netherlands and to the reporter of maternal death of Statistics Netherlands. All maternal deaths reported to the MMMC during or within 1 year after pregnancy between January 1993 and December 2013 in the Netherlands were included in the study. Additional cases were yearly collected after a cross-check with the database of Statistics Netherlands, which collects all vital registration data from the Netherlands.

Maternal death was defined and classified according to the World Health Organization's International Classification of Diseases, 10th revision (ICD-10).[5] Deaths were classified as direct, indirect or fortuitous. A single underlying cause or mode of death was assigned to each case by the members of the MMMC. The underlying cause of death is the disease or injury which results directly in death

or initiates the chain of events leading directly to death. The mode of death is the disease or injury that ends life directly. Substandard care was defined as all care factors which may have resulted in suboptimal care and which had a probable negative influence on the chain of events leading to death. It could be assigned to any person involved in the care of pregnant women and to the pregnant woman herself. Avoidance of such factors did not necessarily mean that death would have been prevented. The standard of care was the care as stated in national guidelines.[6-11] If there was no (appropriate) guideline, the best available evidence was used. The anonymized cases were individually assessed for substandard care factors by the members of the MMMC and discussed at a group meeting for a final decision. When consensus could not be reached, the decision was based on the assessment of the majority of the committee.

A confidential enquiry was completed on each case reported to the MMMC. For each maternal death, data were collected by the MMMC on a standard questionnaire including information concerning general and obstetric histories, as well as the index pregnancy. Sources of information included antenatal charts, laboratory and bacteriological results, pathology and autopsy reports and professional correspondence, if provided. For cases provided by Statistics Netherlands only cause of death and maternal age could be retrieved.

For the current report, we included all deaths caused by cardiovascular disease (including congenital, valvular and ischemic heart disease, pulmonary hypertension, cardiomyopathy, arrhythmias, aortic dissection, myocarditis and infective endocarditis). Furthermore, we included all cases of sudden death (sudden unexplained death syndrome, SUDS, and sudden arrhythmic adult death syndrome, SADS, defined as SUDS with negative pathological and toxicological assessment or sudden death in women with a known arrhythmic disease).[12] We excluded all cases in which maternal mortality occurred more than six months after pregnancy and all cases of mortality due to vascular disease other than aortic or coronary artery disease, such as cerebral vascular accidents or ischemia of the abdominal arteries.

Obstetric and neonatal complications were defined as diagnosed and treated by the responsible physicians and according to definitions in previous papers and included Caesarean section (CS, both planned and emergency), pregnancy induced hypertension, (pre)eclampsia, Haemolysis Elevated Liver enzymes and Low Platelets – (HELLP) syndrome, postpartum haemorrhage, preterm labour, early foetal death (intrauterine death ≤20 weeks of gestation, not induced abortion), offspring death (defined as the total number of stillbirths >20 weeks of gestation and deaths up to 6 months postpartum), neonatal respiratory distress syndrome, preterm birth (<37 weeks of gestation), low birth weight (<2500 grams), occurrence of congenital heart disease (CHD) or other congenital disease in the offspring and Apgar-score <7 (at one and five minutes after birth).[13]

Individual cases, updates and trends have been presented at obstetric meetings in the Netherlands, published in (inter)national journals, national guidelines and as case reports in a Dutch medical journal. Some cases have been included in previous publications concerning vascular dissection and rupture and (indirect) maternal mortality.[2 14]

Statistical analysis was performed using IBM SPSS Statistics Premium' V 22 for Windows (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Continuous data are presented as means with standard deviation or median with IQR or range depending on their distribution. Normality was tested with the Kolmogorov-Smirnov test with Lilliefors' correction. Absolute numbers and percentages were presented for categorical data. Missing data were excluded for analysis.

RESULTS

From January 1993 until December 2013, 96 women died from cardiovascular diseases during their pregnancy in the Netherlands. This results in a maternal mortality ratio from cardiovascular diseases of 2.4 per 100.000 live born children. Baseline characteristics, timing and causes of death of the women who died are provided in figure 1 and table 1. Most women (55%) died during the post-partum period. Care factors contributing to the adverse outcome were reported in 27 cases (28%) (table 2). These factors were completely or partially attributable to the patient in 40%. There was no relation to ethnicity (p=.63). Avoidable care factors contributing to the death had a tendency to be present more often in women with a known history of cardiovascular disease than in women without a history of cardiovascular disease (70%, n=9,vs 40%, n=17, p=.06, OR 3.44, 95% CI 0.91-12.97).

Thirty-four women died during pregnancy. Their offspring all died (n=33, including two twin pregnancies). Fifty-five women died postpartum (58%). There were 3 perinatal deaths in 3 of these women and one early foetal death after successful maternal cardiopulmonary resuscitation. Median timing of delivery was 37+2 weeks (range 22 to 42 weeks), mean birth weight was 2709 grams (SD 914 grams).

Reported obstetric and perinatal complications are presented in table 3. There were no cases of eclampsia or HELLP syndrome. CS (n=10) were performed for maternal indication in 5 planned and 5 emergency CS.

SUDS and SADS

Twenty-seven women died due to unexplained or arrhythmic sudden death, SUDS (n=19) or SADS (n=8).

Two women who died due to SADS were known with cardiac rhythm disorders, in both women contributing care factors were identified. One woman with long QT syndrome had discontinued her beta-blocker therapy against medical advice. The other woman was known with Wolf-Parkinson-White syndrome. She had been arrhythmia-free without medication since six years. There was a delay in referral to a cardiologist when she complained about palpitations during pregnancy.

Autopsy was definitely not performed in 12 of 19 women with SUDS and not performed or not reported to the MMMC in another four cases. Five women had cardiac or non-cardiac underlying diseases that possibly but not definitely may have been related to the sudden death (myocardial infarction and heart failure, aortic valve surgery, left ventricular hypertrophy and anomalous left coronary artery, hyperthyroid disease, hyperemesis with dehydration).

Time of death was during pregnancy in eight and during the post-partum period in 16 women. Intra uterine and early foetal death was reported in seven cases and accompanied maternal death. Delay in hospital referral was reported in one woman. Information about possible contributing suboptimal care factors was missing in 22 cases.

Aortic dissection

Twenty women (21%) died from dissection of the aorta. Most dissections occurred in the 3rd trimester (40%) and post-partum (35%). Pre-existing relevant morbidity was present in eight women (40%): three had a connective tissue disease (18% compared to 0% in women who died due to other CVD, p<.01) and five had pre-pregnancy hypertension (25%). Hypertensive obstetric complications occurred in four women, (pregnancy induced hypertension (n=3) and, pre-eclampsia (n=1)). Overall, seven women had hypertension, pre-existent or pregnancy induced (41% in women with aortic dissection vs. 19% in women who died due to other CVD, p=.052). In eleven cases perinatal death accompanied maternal death. In eight women (40%) suboptimal care factors were identified. In seven cases these involved the presence of signs and symptoms of aortic dissection (including chest or back pain, dyspnoea and circulatory failure) without this leading to proper diagnostic tests and recognition of the diagnosis. Two of these women were misdiagnosed with a psychiatric disorder. In one case the diagnosis was rejected after a false-negative sonography.

Ischemic heart disease

Seventeen women (18%) died from ischemic heart disease. None of these women were known with coronary artery disease. Fourteen women (13% of total maternal deaths) presented with acute myocardial infarction (AMI) during pregnancy. All but one woman presented during the 3rd trimester or post-partum period (1 missing). AMI was caused by coronary dissection (n=4), coronary sclerosis/thrombosis (n=2), or other/unspecified causes. Risk factors for ischemic heart disease were reported in four women (33%). Obstetric events included postpartum haemorrhage (n=3, not related to maternal death) and CS because of pre-eclampsia (n=2). Neonatal death (n=5) accompanied maternal death in 4 cases. In five cases underestimation of the complaints was reported (four times by the doctor, once by the patient). Failure to install proper therapy was described in one patient.

In three women the diagnosis ischemic heart disease was made at autopsy, two of them had presented with heart failure.

Cardiomyopathy

Thirteen women (14%) died from cardiomyopathy. In 43% potentially avoidable contributing care factors were identified.

Peripartum cardiomyopathy

The four women with peripartum cardiomyopathy all died post-partum. One of these pregnancies had been complicated by pre-eclampsia and delivery of a child with a low birth weight at 37 weeks. There were no other obstetric or neonatal complications. In one woman there was a delay in diagnosis, another woman discontinued her medication against medical advice.

Other cardiomyopathy

Ten women died from cardiomyopathy other than peripartum cardiomyopathy. Three had dilated cardiomyopathy (DCM), three arrhythmogenic cardiomyopathy, one hypertrophic cardiomyopathy and one Takotsubo cardiomyopathy after a difficult vaginal delivery. Most women died in the post-partum period (n=8, one missing). Three of them had been diagnosed before pregnancy. Four of the seven women who were not known with cardiomyopathy had a positive 1st degree family history for cardiomyopathy (n=2) or acute death in a young 1st degree relative (<45 years, n=2). Whether or not pre-pregnancy screening had been performed in these women is unknown. Obstetric complications were reported in three pregnancies and included one planned and one emergency CS. Neonatal complications were observed in four pregnancies, including one early foetal death. Contributing care factors that might have been avoided were reported in four cases (44%, one missing) (pregnancy against medical advice (n=2), delay in specialist referral (n=1) and underestimation of the complaints by the patient (n=1)).

Seven women (7%) died from myocarditis, five during pregnancy and one post-partum. None of the women had a history of cardiac disease. There were no obstetric complications. Maternal death was accompanied by offspring death in three women. In one woman and a delay in referral to a specialist was reported.

Other CVD

Valvular heart disease and prosthetic heart valves (PHV)

Four women died due to native valvular heart disease, in three cases the woman became pregnant against medical advice. One woman, known with severe aortic and mitral regurgitation, had refused cardiac surgery and died suddenly during the post-partum period. A woman with congenital aortic stenosis and mitral regurgitation died due to decompensated aortic stenosis in the third trimester, her foetus also died. Two women died due to complicated endocarditis.

Four women (4%) died due to complications of their PHV. Three deaths were attributable to mechanical PHV thrombosis. All women were treated with LMWH at the time of valve thrombosis. One woman died two and a half month after cardiogenic shock and resuscitation due to a thrombosed aortic PHV in the second trimester of pregnancy. Her foetus died as well. Another woman had a thrombosis of her mitral PHV in the third trimester of pregnancy. Acute re-surgery was complicated by cardiac tamponade, sepsis, and intracranial haemorrhage, and brain stem herniation. The third woman died in the 1st trimester due to heart failure, a thrombosed mitral PHV was observed on autopsy. Substandard care was not reported by the MMC. Whether or not anti-Xa measurements were performed during LMWH treatment was not reported to the MMC. These cases of PHV thrombosis occurred in 2002, 2008 and 2008.

One other PHV related death occurred due to haemorrhagic complications of anticoagulation therapy during the 3rd trimester. She died due to pulmonary haemorrhage while she was anticoagulated with a vitamin K antagonist (INR 7.5). This woman was pregnant against medical advice. Her child died as well.

Congenital heart disease and pulmonary hypertension

One woman died from CHD and one from pulmonary hypertension. A woman with a Fontan circulation died due to cardiovascular collapse post-partum after a CS for a maternal non-cardiac indication. She had been advised against pregnancy.

A 28 year old primiparous woman with systemic lupus erythematosus died 3 months post-partum due to heart failure due to previously unrecognized pulmonary hypertension.

DISCUSSION

Our study showed that the majority of cardiovascular maternal deaths in the Netherlands in the last twenty one years was caused by aortic dissection, ischemic heart disease, cardiomyopathies and SUDS/SADS. Interestingly, these causes are very similar to the causes of cardiovascular maternal death in the UK in the last three years (figure 1).[15] Both aortic dissection, ischemic heart disease and cardiomyopathy are rare diseases in young pregnant women, often presenting acutely and unexpectedly. Additionally, the presentation in pregnant women can be atypical or symptoms may be attributed to normal pregnancy discomforts. This likely contributes to the high mortality of these diseases in pregnant women. Many deaths occurred postpartum. Physicians and first care providers should realize that also after the early postpartum period women remain at increased risk of fatal pregnancy-related complications.

Unfortunately, the incidence of possibly avoidable care factors that may have contributed to the adverse outcomes did not significantly decrease in the last decade. This may be partly attributable to the slight rise in patient related factors, which underlines the importance of adequate pre-pregnancy counselling of women with known heart disease. A main contributing health care provider related care factor was failure to recognize the diagnosis timely. This calls for extended education of caregivers concerning recognition and treatment of cardiac diseases during pregnancy and the post-partum period.[2 3]

SUDS and SADS

As in other recent reports, the largest group of contemporary cardiac maternal deaths were unexplained sudden deaths (SUDS and SADS).[1] In our study autopsy was frequently not performed in those women, which is unfavourable for medical knowledge and science and may in some cases even be legally disputable in the Netherlands. Withholding autopsy was not considered substandard care by the MMC during the studied period since it did not influence the maternal death. However, it may contribute to suboptimal care for the families of these deceased mothers because positive findings at autopsy are facilitating family screening and may eventually contribute to prevent further deaths in these families. Four women with SUDS had conditions which may have induced cardiac arrhythmias. Women with known cardiac rhythm disorders should be under cardiologic supervision before and during pregnancy. In some women, a switch in anti-arrhythmic medication to avoid foetal risk associated with some anti-arrhythmic medication may be necessary.[16] When a woman with a cardiac rhythm disorders experiences either palpitations, dizziness, dyspnoea or chest pain during pregnancy, she should be referred without delay to a cardiologist for further evaluation.

Aortic dissection

Aortic dissection during pregnancy is rare but has a high case fatality rate of 83%.[17] The diagnosis can be challenging and it should be considered as a possible cause of thoracic pain, especially when risk factors for aortic dissection (e.g. connective tissue disease or hypertension) are present, as in 50% of our population.[18] Despite the presence of symptoms indicative of aortic dissection the diagnosis frequently was not made.[19] Interestingly, two women were misdiagnosed with a psychiatric disorder, which has been described as a pitfall in the presentation of aortic dissection in emergency medicine.[20-22] Sonography alone is insufficient to exclude aortic dissection according to current guidelines, as is illustrated by one of our cases.[19] We recommend that aortic dissection should be considered in every pregnant woman with risk factors for aortic dissection and unexplained chest pain, back pain, also when combined with unexplained neuropsychiatric symptoms. EKG-gated CT-scanning of the chest is indicated when there is a reasonable suspicion for aortic dissection.

Ischemic heart disease

IHD was the second most frequent cause of maternal cardiac death, in line with other reports.[1] Pregnancy is known to increase the risk of manifestations of IHD 3-4 fold.[23] Acute coronary syndromes are known to be more prevalent during late pregnancy.[24] The maternal mortality ratio is 3-11% and maternal morbidity, foetal mortality and morbidity rates are also high.[17 24 25] Consistent with other reports we found coronary dissection to be a frequent cause of IHD.[24] Risk factors for coronary artery disease are often present, especially in women with atherosclerotic disease.[24] Proper recognition of the diagnosis appeared difficult and severity of complaints was often underestimated. In pregnant women with chest pain it is insufficient to exclude the differential diagnosis of pulmonary embolism and aortic dissection, and IHD should be ruled out with EKG and biomarker tests. It is important to realize that IHD can also have an atypical presentation with symptoms such as syncope or dyspnoea.

Cardiomyopathy

A recent national study found a high incidence of cardiovascular morbidity due to cardiomyopathy during pregnancy but with a relatively low case fatality rate.[17] In our study cardiomyopathy was the third most frequent cause of maternal cardiac death. Four women died due to peripartum cardiomyopathy, which is known for its high mortality risk up to 30%.[26] Care factors related to the adverse outcome were mostly patient-related. Interestingly, one woman died from Takotsubo cardiomyopathy, which is a rare diagnosis during pregnancy. It is a stress-related cardiomyopathy presenting with severe heart failure and chest pain, with typical wall motion abnormalities of the apical region (apical ballooning).

During pregnancy it has been mainly related to CS or pre-eclampsia, however in our patient the Takotsubo cardiomyopathy occurred after a difficult vaginal delivery.[27] One woman died due to hypertrophic cardiomyopathy, a condition usually well tolerated during pregnancy with low mortality rates (0.5%).[28]

Half of the women who were not known with (non-pregnancy related) cardiomyopathy before pregnancy had a positive family history for cardiomyopathy or early sudden death. These are the women who may benefit from pre-pregnancy screening and cardiac evaluation including echocardiography. Physicians should always consider family screening in first degree relatives of patients with cardiomyopathy or early sudden death. Furthermore, in newly pregnant women a family history should be taken and women with a positive family history for cardiomyopathy and/or acute death should be evaluated by a cardiologist early during the pregnancy when screening pre-pregnancy has not been performed. Women with known cardiomyopathy should be under tight medical supervision during pregnancy as well as the post-partum period.

Other CVD

Valvular heart disease is a frequent cause of cardiovascular morbidity during pregnancy in the Netherlands but has relatively low case fatality rates.[17] However, the cases described illustrate that the risk of severe native valvular disease should not be underestimated. Most women with valvular disease who died had been advised against pregnancy. Women who are advised against pregnancy for medical reasons may need intensive psychological and medical support and should be advised about safe and effective contraception. In women with a mechanical PHV, the main concern during pregnancy is balancing the risk of PHV thrombosis (which is relatively high with LMWH therapy) with the risk of bleeding and the risk of embryopathy (which only exists with warfarin therapy during the first trimester, and not with LMWH therapy). Thrombosis and bleeding were causes of death in our population. All women who died due to PHV thrombosis were anticoagulated with LMWH. A high maternal death rate (9%) in women with a mechanical PHV has recently been described in the UK and seemed related to LMWH.[29] Given the higher risk of valve thrombosis, current European and American guidelines advise that LMWH therapy should be limited to the first trimester and the last month of pregnancy, and should only be used when frequent anti-Xa monitoring with dose-adjusting is available. In women needing a low dose of VKA it should be considered to continue the VKA throughout pregnancy.[30 31] Data concerning anti-Xa monitoring were not available to the MMC and not taken into account in the assignment of substandard care. It is important to realize that anticoagulation dose can change during pregnancy and therefore monitoring of anticoagulation effect is more frequently necessary than outside pregnancy.[30 31]

Though CHD is the most frequent underlying maternal heart disease in the western world, only one death occurred, in a woman advised against pregnancy. The woman who died due to unrecognized pulmonary hypertension was known with a condition associated with pulmonary hypertension (SLE). Pre-pregnancy evaluation in these conditions may influence pre-pregnancy advice while current guidelines still advise against pregnancy in women with PH because of high maternal mortality and morbidity rates.[31]

LIMITATIONS

Data and analysis were limited by the amount of available data delivered to the MMMC. While we choose to cross check cases of maternal death with vital data of Statistics Netherlands to prevent missing a case of maternal we deprived ourselves from additional data which could not be provided or retrieved by Statistics Netherlands. The presence of missing data could therefore not be prevented. Finally, while expert help was consulted when needed, a cardiologist and acute care specialist such as an emergency physician were not systematically involved in the evaluation of cases of maternal death by the MMC.

CONCLUSION AND KEY RECOMMENDATIONS

- Maternal cardiovascular mortality rates are low in the Netherlands. In a significant minority possibly avoidable care factors (attributable to the patient or the health care provided) contributed to maternal adverse outcome. Our data result in several recommendations that may contribute to further improvement of care for pregnant women with cardiovascular diseases.

- Women with known heart disease should be advised in pursuing pregnancy following current guidelines and be closely monitored by a cardiologist and a perinatologist with expertise in the field of pregnancy and heart disease.

- It is important to be aware that a post-partum period is a vulnerable period for maternal cardiac death.

- Not all chest pain in pregnant women is caused by pulmonary embolism. Chest pain or back pain especially when hypertension or a family history of connective tissue disorders is present, may indicate aortic dissection and a chest CT should be considered.

- Ischemic heart disease should be considered in pregnant women with chest pain and an EKG and cardiac biomarker test (Troponin) should be performed.

- Women with a positive family history for cardiomyopathy and/or acute death should be evaluated preconceptionally by a cardiologist.

- Women with known cardiomyopathy should be under tight medical supervision during pregnancy as well as the whole post-partum period.

- Women with a heart valve prosthesis should be treated during pregnancy in an expert centre according to guidelines under close anti-Xa or INR (self) monitoring depending on type of anticoagulation, in order to prevent PHV thrombosis or bleeding complications.[30-32]

- Autopsy should always be performed in women who die from unexplained causes during pregnancy or in the post-partum period.

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TABLES AND FIGURES

Table 1. Baseline characteristics, timing and causes of death for the women who died during pregnancy or in the post-partum period due to cardiovascular diseases in 1993-2013 in the Netherlands.

Period	Total (1993-2013)	1st decade (1993-2003)	2nd decade (2003-2013)*
N (women)	96	36	60
Age (mean years, SD)	31,6 (5,8)	30,4 (6,1)	32,4 (5,6)
Gravidity (median, range)	2 (1-11)	2 (1—11)	2 (1-7)
Parity (median, range)	1 (0-5)	1 (0-5)	1 (0-4)
Timing of death			
During pregnancy, 1st trimester	7 (7%)	2 (6%)	5 (8%)
2nd trimester	11 (11%)	4 (11%)	7 (12%)
3rd trimester	16 (16%)	8 (22%)	8 (13%)
During post-partum period, <21d	22 (22%)	8 (22%)	14 (23%)
>21d	33 (33%)	11 (31%)	23 (38%)
Unknown	7 (7%)	3 (8%)	3 (5%)
Ethnicity			
Dutch	60 (63%)	21 (58%)	39 (65%)
Surinamese/ Dutch Antilles	9 (9%)	6 (17%)	3 (5%)
Turkish	5 (5%)	3 (8%)	2 (3%)
Other	6 (6%)	3 (8%)	3 (5%)
Unknown	16 (17%)	3 (8%)	13 (22%)
Cause of death			
SUDS/SADS	27 (28%)	7 (19%)	20 (33%)
Aortic dissection	20 (21%)	7 (19%)	13 (22%)
Ischemic heart disease	17 (18%)	9 (25%)	8 (13%)
of which acute myocardial infarction	*14 (15%)*	*7 (19%)*	*7 (12%)*
Cardiomyopathy, not pregnancy related	8 (8%)	3 (8%)	6 (10%)
pregnancy related	4 (4%)	2 (6%)	2 (3%)
Myocarditis	7 (7%)	3 (8%)	4 (7%)
Unknown	1 (1%)	-	1 (2%)
Other	12	5	7
PHV complications	4 (4%)	2 (6%)	2 (3%)
Valvular heart disease (no PHV)	4 (4%)	2 (6%)	2 (3%)
Congenital heart disease	1 (1%)	1 (3%)	-
Pulmonary hypertension	1 (1%	-	1 (2%)

VF = ventricular fibrillation, PHV= Prosthetic heart valve, SADS = sudden adult death syndrome, SUDS = sudden unexplained death syndrome. *includes the year 2003.

Table 2. Possibly avoidable care factors contributing to maternal death in women who died due to cardiovascular disease during 1993-2013 in the Netherlands.

Period	Total (1993-2013)	1st decade (1993-2003)	2nd decade (2003-2013)
Total reported cases of substandard care (N,%)	*27 (28%)*	*12 (33%)*	*15 (25%)*
Healthcare provider related			
Diagnosis not recognized by doctor or midwife	12 (44%)	6 (50%)	6 (40%)
Delay in referral to specialist	4 (15%)	2 (17%)	2 (13%)
Patient related			
Pregnancy initiated against medical advice	6 (22%)	2 (17%)	4 (27%)
No acknowledgment of complaints by patient	3 (11%)	1 (8%)	2 (13%)
Discontinuation of medication against medical advice	2 (7%)	1 (8%)	1 (7%)

Table 3. Obstetric and perinatal complications in pregnancies in women who died due to cardiovascular disease in the Netherlands.

Period	Total (1993-2013)	1st decade (1993-2003)	2nd decade (2003-2013)
Total reported pregnancies with obstetric complications (N,%)	33 (34%)	9 (25%)	24 (39%)
Planned CS	7 (7%)	1 (6%)	6 (18%)
Emergency CS	10 (19%)	4 (24%)	6 (18%)
Abortion	1 (2%)	1 (5%)	0
PIH	4 (5%)	2 (8%)	2 (4%)
Pre-eclampsia	6 (8%)	2 (8%)	4 (8%)
PPH	7 (13%)	2 (11%)	5 (15%)
Hyperemesis (pregnancy induced)	2 (3%)	-	2 (4%)
Gestational DM	1 (1%)	0	1 (2%)
Preterm labor	3 (6%)	1 (6%)	2 (6%)
Total reported pregnancies with offspring complications (N,%)	55 (55%)	22 (60%)	33 (52%)
Early fetal death	15 (17%)	5 (16%)	10 (19%)
accompanied by maternal death (% of total)	*14 (93%)*	*5 (100%)*	*9 (90%)*
Perinatal death	22 (27%)	10 (35%)	12 (23%)
accompanied by maternal death (% of total)	*19(86%)*	*9 (90%)*	*10 (83%)*
Prematurity	17 (35%)	7 (47%)	10 (29%)
Low birth weight	12 (29%)	4 (29%)	8 (29%)
NRDS	1 (2%)	1 (7%)	-
APGAR <7	1 (3%)	-	1 (4%)

CS = Caesarean section, DM = Diabetes Mellitus, NRDS= , neonatal respiratory distress syndrome, PIH= pregnancy induced hypertension, PPH= post-partum hemorrhage. Missing data are excluded for analysis except for total reported numbers of complication.

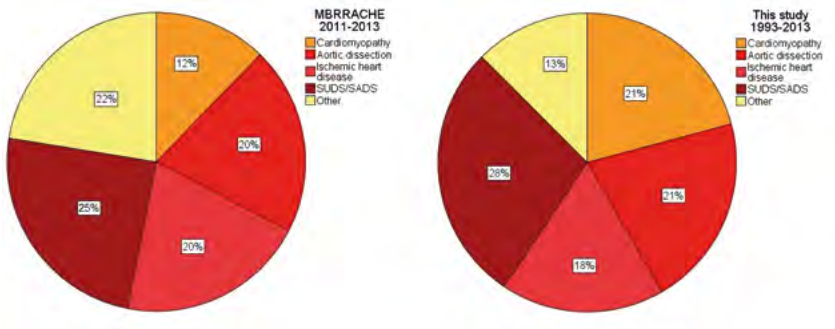
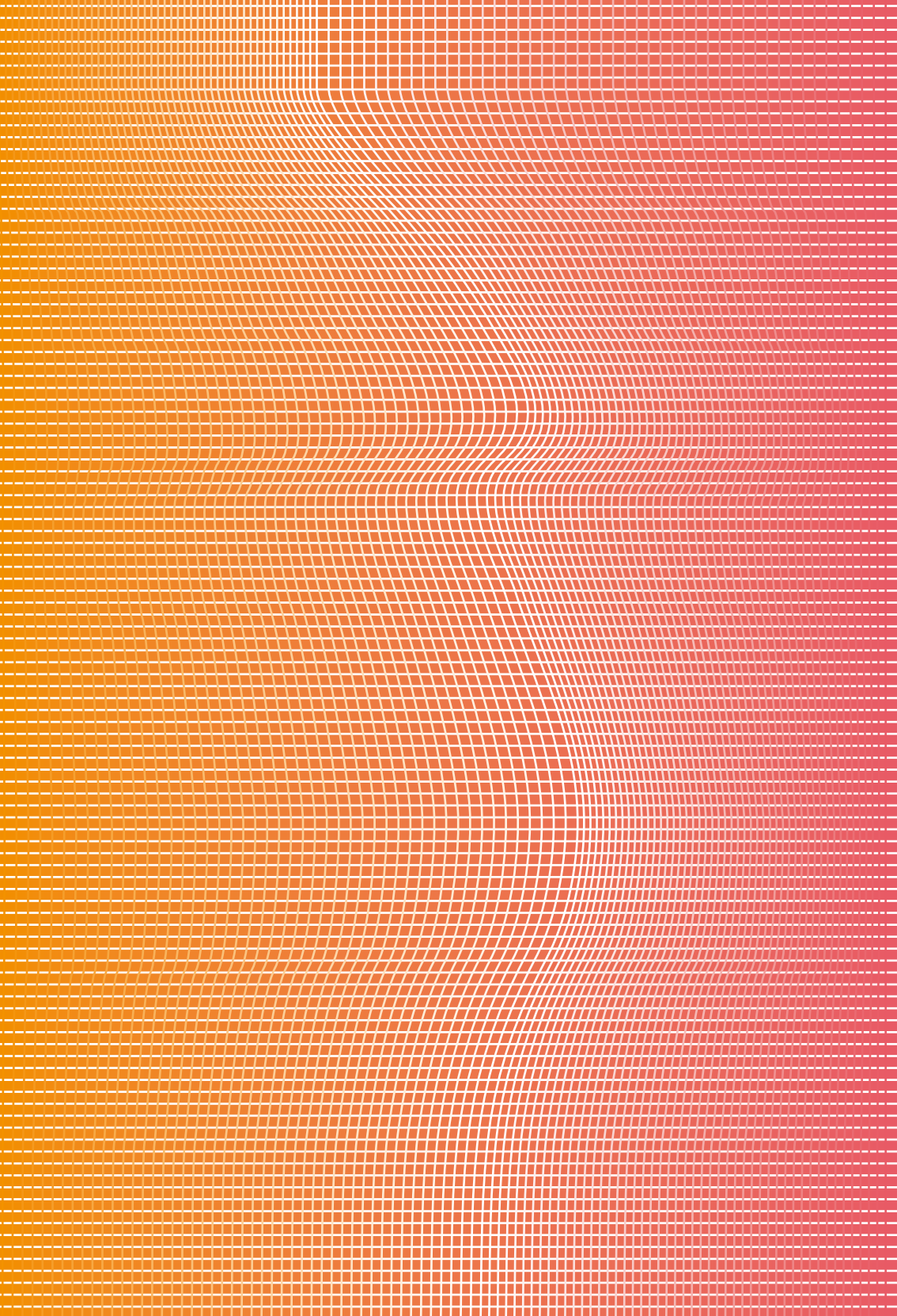


Figure 1. CS = Caesarean section, DM = Diabetes Mellitus, NRDS= , neonatal respiratory distress syndrome, PIH= pregnancy induced hypertension, PPH= post-partum hemorrhage. Missing data are excluded for analysis except for total reported numbers of complication.



3

Ischaemic heart disease during pregnancy or postpartum: systematic review and case series

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Neth Heart J. 2015 May;23(5):249-57. doi: 10.1007/s12471-015-0677-6.

ABSTRACT

The risk of manifestations of ischaemic heart disease (IHD) in fertile women is elevated during pregnancy and the post-partum period. With increasing maternal age and a higher prevalence of cardiac risk factors, the incidence of IHD during pregnancy is rising. However, information in the literature is scarce. We therefore performed a retrospective cohort study and systematically reviewed the overall (1975–2013) and contemporary (2005–2013) literature concerning IHD presenting during pregnancy or in the post-partum period. We report two cases of IHD with atypical presentation during pregnancy or post-partum. In our review, we describe 146 pregnancies, including 57 contemporary cases (2005–2013). Risk factors for IHD were present in 80 %. Of the cases of IHD, 71 % manifested in the third trimester or the post-partum period, and 95 % presented with chest pain. The main cause was coronary dissection (35 %), or thrombus/emboli (35 %) in the more contemporary group. Maternal mortality was 8 % (6 % in the contemporary group), and the main cardiac complication was ventricular tachycardia ($n = 17$). Premature delivery rate was 56 %, and caesarean section was performed in 57 %. Perinatal mortality was 4 %. In conclusion, IHD during pregnancy or in the post-partum period has high maternal mortality and morbidity rates. Also, premature delivery and perinatal mortality rates are high.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in men and women in the western world.[1-3] Fifty percent is due to ischaemic heart disease (IHD).[1] Though pre-menopausal women are relatively protected against atherosclerosis by their hormonal status, the risk of manifestations of IHD is increased during pregnancy and in the postpartum period.[4-6] This is due to cardiovascular and hemodynamic changes and hypercoagulability occurring during pregnancy.[7-9] CVD is the leading cause of indirect maternal death during pregnancy in western countries, with IHD including acute myocardial infarction (AMI) as a frequent underlying disease.[10 11] Previous studies estimated an incidence of IHD during pregnancy of 2.8 to 6.2 per 100.000 deliveries, 3 to 4 times higher than the incidence found in non-pregnant women of reproductive age.[4 12]

Increasing maternal age and deteriorating lifestyle choices lead to a higher incidence of cardiac risk factors. Consequently the incidence of IHD during pregnancy will increase worldwide.[13 14] However, information about IHD presenting during pregnancy is scarce. Incomplete information is available concerning aetiology of IHD, time of presentation, and maternal and offspring outcomes.[4-6] We therefore present two cases of women in whom IHD presented during pregnancy or the postpartum period. Furthermore we systematically reviewed the literature about IHD presenting during pregnancy or in the postpartum period. Additionally we will present a significant subset of contemporary cases separately.

METHODS

For our case series we performed a retrospective cohort study. All data were obtained by systematic search of databases and matching of cardiology department and gynaecology department databases in the University Medical Centre Groningen, Amsterdam Medical Centre and University Medical Centre Utrecht, all in the Netherlands. Diagnostic database matching codes were Angina Pectoris, STEMI, non-STEMI, follow-up after myocardial infarction, follow-up after CABG and follow-up after PCI. Women who presented with a first manifestation of IHD after conception until six weeks postpartum in a 10-year period (2002 to 2012) were included, regardless of duration, outcome and course of the pregnancy. IHD was defined according to ESC/ACC/AHA criteria.[15] Women with significant congenital coronary abnormalities were excluded. Retrospective cohort studies do not need to be approved by the institutional review board in the Netherlands.

For our systematic review we used the PRISMA-statement protocol.[16] We researched the *MedLine public database* for all studies dated until 10-04-2013. Search terminology was Myocardial ischemia and Pregnancy, both in

Mesh terms ("Myocardial Ischemia"[Mesh]) AND "Pregnancy"[Mesh]) and full text (Myocardial ischemia AND pregnancy). The filters Humans, Case Reports, Meta-Analysis, Clinical Trial, Randomized Controlled Trial, Dutch, English, German, Female, MEDLINE, Adult: 19+ years and Adolescent: 13-18 years were activated. We only included studies written in English, German and Dutch to reduce misinterpretation of data. Systematic reviews were excluded but new cases described in reviews were included. Cases described before 1975 were excluded. We included all online available articles, either from open access publishing and availability provided by the University Medical Centre Groningen. Articles describing myocardial ischaemia before pregnancy, ischaemia induced by medication or pheochromocytoma or caused by Kawasaki's or Takotsubo syndrome were excluded.

In both our case series as well as our systematic review we collected data concerning the timing, cause and treatment of IHD, comorbidities, risk factors for IHD and maternal cardiac and obstetric outcome as well as offspring outcome. Prematurity of the foetus was defined as birth <37 weeks, low birth weight was defined as <2500 grams, small for gestational age is defined as birth weight <10th percentile. Perinatal mortality is defined as offspring death from 20 weeks of gestation up to 7 days post-partum. We described cases published in or after 2005 and not included in the latest review[6] separately and we compare these contemporary cases to previous literature. Statistical analysis was performed using IBM SPSS Statistics Premium' V 20 for Windows (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Missing data were excluded for analysis. Continuous data are presented as means with standard deviation or median with IQR depending on their distribution. Absolute numbers and percentages were presented for categorical data. For comparison of categorical variables the Fisher exact test or Chi-square test was used.

RESULTS

Case series

We identified two cases matching our inclusion and exclusion criteria.

Our ***first case*** is a 25-year old woman of Hispanic descent, with one previous miscarriage (G2P0). The patient was severely obese with a BMI of 39. She had a history of a transient ischaemic attack (TIA), suspected antiphospolipid syndrome, and mitral valvuloplasty for mitral regurgitation due to non-bacterial endocarditis. She was referred to the cardiologist for pre-pregnancy counselling. When she was pregnant, her vitamin K antagonist was replaced by acetyl salicylic acid and full dose low molecular weight heparin during pregnancy until the fifth day postpartum. At 27 weeks of gestation she presented with complaints of upper

abdominal pain. She was diagnosed with pre-eclampsia complicated by HELLP syndrome (Haemolysis Elevated Liver enzymes and Low Platelet; ALAT 143 U/l, thrombocytes 128 10^9/l). Foetal ultrasonography showed normal growth and foetal condition judged by cardiotocography (CTG) was well. The patient was treated with labetalol and magnesium sulphate (MgSO4). At 29+3 weeks of gestation, her condition worsened and a Caesarean section was performed. She delivered a baby girl of 1067 grams (50th percentile) with an Apgar score of 6 at 5 minutes. The neonate had to be admitted to the neonatal intensive care unit (NICU) because of prematurity. Three days postpartum the mother presented with syncope. Chest pain was not reported. Electrocardiographic (ECG) monitoring showed ST-segment depression and Q-waves, suggesting inferolateral AMI, which was confirmed by elevated troponin-T (5,96 ug/l; normal <0,014 ug/l). Her coronary angiogram (CAG) showed no abnormalities. The AMI was presumably caused by a thrombus, embolism or coronary spasm. Both mother and neonate survived. Her medication was upgraded to a beta-blocker, ACE-inhibitor, statin, acetylsalicylic acid and vitamin K-antagonist. Echocardiography at 6 months showed a mildly reduced left ventricular function. The diagnosis of antiphospolipid syndrome was confirmed.

Our ***second case*** is a 42 year old woman, G1P0. She had a history of insulin dependent DM, pulmonary embolism and a positive family history for IHD. She was referred to a university hospital by an obstetric clinic at 15 weeks of gestation because of an episode of ventricular tachycardia. Her ECG suggested anterior AMI which was confirmed by raised Troponin (37,77 ug/l) and Creatin Kinase (2239 U/l) levels. Her CAG revealed atherosclerotic occlusion of the left main coronary artery. She was treated with stenting of the left coronary artery and medically with acetylsalicylic acid, B-blocker, clopidogrel and subcutaneous heparin. At 37 weeks of gestation intrauterine growth retardation and placental insufficiency was suspected... The decision was made to perform an elective Caesarean section. She delivered a live born neonate at 37 + 5 weeks. Neonatal Apgar score at 5 minutes was 10, birth weight was 2405 grams, which is at the 5th percentile for gestational age. Histological examination of the placenta showed a small placenta (weight <10th percentile), with diffuse ischaemia, consistent with placental insufficiency. A statin was added to the maternal medical regimen during the postpartum period. Maternal ventricular function remained normal during 6 months of follow up. A stress test and nuclear scan revealed no signs of recurrent ischaemia. The neonate did well.

Systematic review

We found 128 articles describing IHD presenting during pregnancy and in the postpartum period, with a total of 146 pregnancies, including 6 twin-pregnancies and one triplet pregnancy. Inclusion is schematically presented in *Figure 1.* We excluded several studies for statistical analysis because of incomplete individual

data concerning both cardiac and obstetric outcomes. The results of these studies are summarized and compared with our results in a table and are discussed in our discussion section.[4-6 17-19] All articles included were published between 1978 and 2012 and are presented in supplemental *Table S1*, which is available online.

Baseline characteristics

Baseline maternal characteristics are found in *Table 1.*

IHD, characteristics and treatment

Characteristics of IHD during pregnancy, delivery or in the post-partum period are reported in *Table 2.* Comparison with other studies and characteristics of the contemporary group can be found in *Table 3.* All women experienced symptoms suggestive of AMI. In 89% ST-segment deviation was seen on ECG. In contrast to the overall group of women with IHD during pregnancy, where dissection was the most prevalent cause of IHD, in the contemporary group (N=57) the incidences of thrombus or embolism and of dissection were comparable (20 versus 18 women) (Table 2). Ninety-three percent of the women who had AMI due to atherosclerosis had one or more risk factors for IHD, compared to 43% of the women who had AMI caused by coronary dissection (p<0,001) and 68% of women with thrombus or emboli (p<.01).

The aetiology differed depending on the time of presentation during pregnancy (Figure 2). Eighty-seven percent of the cases of coronary dissection presented in the third trimester or postpartum period. Atherosclerosis peaked in the third trimester (42% of all cases of atherosclerosis), whereas AMI with normal coronaries or caused by thrombosis or emboli was independent on the stage of pregnancy. Most women were treated non-invasively (n=50) or with percutaneous intervention (PCI) (n=47). Twenty-two women had coronary artery bypass (CABG) surgery, in 34 women therapy was not clearly reported.

Maternal outcome

Comparison with other studies and characteristics of the contemporary group can be found in *Table 2.*

Cardiac outcome

Seventeen women had had an episode of ventricular tachycardia (VT), mostly as a presenting symptom. Additionally, six women suffered (an episode of) cardiac arrest. In six women IHD was complicated by heart failure, cardiogenic shock occurred in one woman. Ten women had to be intubated during hospitalization, of whom 4 did not survive. In total, 11 deaths were reported (8 percent). We found 6% mortality in the contemporary group, compared to 9% in the group published before 2005 (p=0,337).

Obstetric outcome

Hypertensive disorders during pregnancy were reported in 28 women (18%), progressing to (pre-) eclampsia in 15 women (10%) and HELPP syndrome in 3 (2%) women. These pregnancy related hypertensive disorders were not more frequently found in women with coronary artery dissection. Delivery was mainly by C-section (57%). The C-section rate was not significantly different in women who presented with AMI during pregnancy (62%) compared to women who had their AMI postpartum (44%, p=0.08). In 4 women postpartum haemorrhage was described.

Late complications

In 49% of the women 6 month follow-up was reported. Sixty-four percent of these women had no complications during follow up, in 21% a reduced cardiac function was reported. One woman needed a heart transplantation for progressive cardiac dysfunction. A few reported recurrent angina (n=5) or coronary (pseudo) aneurysm (n=2).

Offspring outcome

Offspring outcome is summarized in *Table 3*. Perinatal mortality was 4%. Reported causes of mortality included maternal mortality (n=2), non-cardiac congenital malformations, prematurity and suspected reduced placental perfusion during cardiopulmonary bypass surgery. Overall median time of delivery was 36 weeks (IQR 34-38). Fifty-six percent of the neonates were delivered prematurely (n=55), which was significantly related to a higher rate of Caesarean section (p=0,012). Prematurity rate was 54% in IHD manifesting during pregnancy and 60% in IHD manifesting during delivery or in the postpartum period. Mean neonatal birth weight was 2645 grams (SD 932 grams), and around the 50th percentile for gestational age in almost all neonates. Low birth weight was reported in 19 patients (missing data in n=107). Only one neonate was small for gestational age. Nine neonates were reported to be admitted to the neonatal intensive care unit. The main reason was prematurity.

DISCUSSION

In this case series and review we add a significant number of new cases compared to previous reviews[6,17], including 57 contemporary cases published after 2004. Our review also adds more detailed data concerning aetiology of IHD and maternal and offspring outcome. Our review confirmed that IHD is rare in pregnancy. Pregnant women with IHD present mostly with chest pain (95%) in the 3rd trimester or postpartum period. Risk factors are invariably present in atherosclerotic disease but less often in thrombotic disease and coronary dissection. Maternal and foetal complication rates, including maternal mortality, are high.

Though IHD is the most common cause of maternal cardiac death in the UK, the estimated incidence of non-fatal IHD in the UK is only 0.7 per 100.000 maternities.[11 20] Since we only found two cases of IHD during pregnancy in our systematic search of three large university hospital databases, IHD presenting during pregnancy is also rare in the Netherlands. This is in line with a recent prospective Dutch study that reported an incidence of 0,005%.[18] In a worldwide registry describing 1321 pregnancies in women with heart disease, only 4 women with a first manifestation of IHD were reported.[19]

Risk factors

Risk factors for IHD were present in both women in our case series and in the majority of the women in our review. This is in line with previous literature.[4-6 17-19] Also, this indicates a large impact of life style factors on IHD during pregnancy, as also described in the UK maternal death report.[11] In line with a recently published study in Japanese women, we observed less risk factors in women with coronary artery dissection or thrombus/emboli than in women with atherosclerosis as a cause of AMI, suggesting a different pathophysiology.[17]

IHD, characteristics and treatment

Women in our review had a relatively high age compared to the average age at time of pregnancy in the United States.[21] This is comparable to previous literature.[5 6 19] Coronary dissection is rare outside pregnancy, but it was the main cause of IHD in the women in our review. However, in our more recent cases thrombo-embolic coronary events were seen equally frequently. Thrombo-embolic events may be largely attributed to pregnancy and its hypercoagulable state. Relatively high rates of coronary dissection during pregnancy have previously been described.[17] In line with previous studies, most cases of AMI presented in the third trimester and postpartum period.[4 5 17] Especially coronary dissection peaked in these periods, which may be explained by progressive connective tissue weakening and therefore susceptibility for dissection in late pregnancy. Pregnancy related hypertensive disorders did not seem to contribute to the high incidence of coronary dissection, nor did inherited connective tissue diseases.

In contrast to the atypical presentation of our 2 cases, in our review chest pain was the main presenting symptom of IHD. Most of the cases of AMI in our review could be detected on ECG. In the UK maternal death report substandard quality of care was observed in 46% of the women who died due to IHD. This often included delay of cardiac evaluation since IHD was not considered as a possible diagnosis. Delayed recognition of IHD during pregnancy was also described in a recent Dutch study.[18] In pregnant women with chest pain, especially when they have risk factors, IHD should be considered and an ECG and laboratory investigation should be performed.

Maternal outcome

A relatively large percentage of women in our systematic review presented with serious complications directly due to AMI, including heart failure, a complication frequently seen in pregnant women with cardiac disease.[19 22] In line with previous literature, mortality rate during pregnancy in women with IHD was higher than in pregnant women with cardiac disease overall.[6 5 17 19] The slightly lower mortality rate in contemporary cases may be explained by improvement of coronary care.

Pregnancy related hypertensive disorders, found to be associated with IHD during pregnancy, were seen more frequently compared to pregnant women with non-ischaemic heart disease.[19 23-25] We observed a very high Caesarean section rate of 57%, that was even higher in contemporary cases. This is higher than the Caesarean section rate in healthy pregnant women (21%),[26] higher than in a previous review[6] and higher than in women with congenital or valvular heart disease (38% and 42%). However, Caesarean section rate was comparable to women with cardiomyopathy (58%) or known IHD (60%).[19] The high Caesarean section rate was related to the high rate of premature deliveries. This high premature delivery rate and high premature C-section rate may be due to several factors, such as the high rate of hypertensive disorders or maternal cardiac reasons for early pregnancy termination. Also, they may possibly be related to physicians' reluctance for vaginal delivery in women with a recent myocardial infarction. Postpartum haemorrhage was described in 3% of the women. This is comparable to women with known cardiac disease and only slightly more than in the general population.[23 27-31]

Offspring outcome

Perinatal mortality was increased at 4% and mainly attributable to maternal death and prematurity. Prematurity rate was 3.4 to 13.2 times higher compared to the prematurity rates in healthy pregnant women.[32-35] Furthermore, it was even high compared to women with non-ischaemic heart disease.[19 23 36] A high rate of induced early deliveries may be part of the explanation. However, prematurity rate was comparable in IHD manifesting during pregnancy to IHD manifesting during labour or in the postpartum period, suggesting an additional mechanism for the high prematurity rates. Interestingly, in contrast to reports in women with non-ischaemic heart disease, the incidence of small for gestational age was not elevated.[25 36 37]

LIMITATIONS

By only including online available articles and articles in English, Dutch or German we may have missed data. In our review analysis was performed by

excluding missing data, which might have led to deformation of results. This is particularly important when missing data were abundant (i.e. cardiac function during follow up). Also, publication bias and selective reporting within studies which could affect the cumulative evidence could not be minimized. Because follow-up was insufficiently reported and limited, (late) maternal complications including death may have been underestimated.

CONCLUSIONS

In contrast to the atypical presentation in our case series, IHD during pregnancy mainly presents with chest pain and during the third trimester or the postpartum period. The main causes are coronary dissection and, in more recent cases, thrombus and embolism. Risk factors for IHD were present in most women with atherosclerotic disease, but less often in women with coronary dissection or thrombosis/embolism. IHD during pregnancy or the post-partum period has a high maternal mortality rate and high maternal cardiac complication rates. Perinatal mortality and premature birth are increased in women with IHD and related to high Caesarean section rate. Clinicians should seriously consider IHD when a pregnant women presents with chest pain, in particular in women with known risk factors for IHD. However, atypical presentation (i.e. collapse) is also possible.

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TABLES AND FIGURES

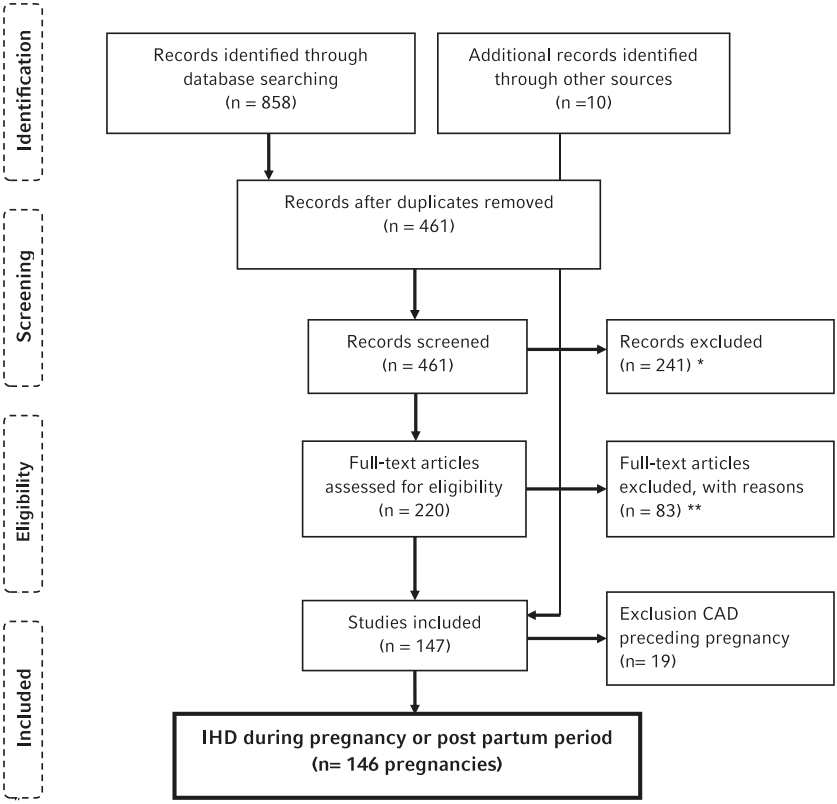

Figure 1. Flow diagram inclusion of literature; IHD= Ischaemic heart disease, * exclusion based on abstract and title, ** not available articles were excluded.

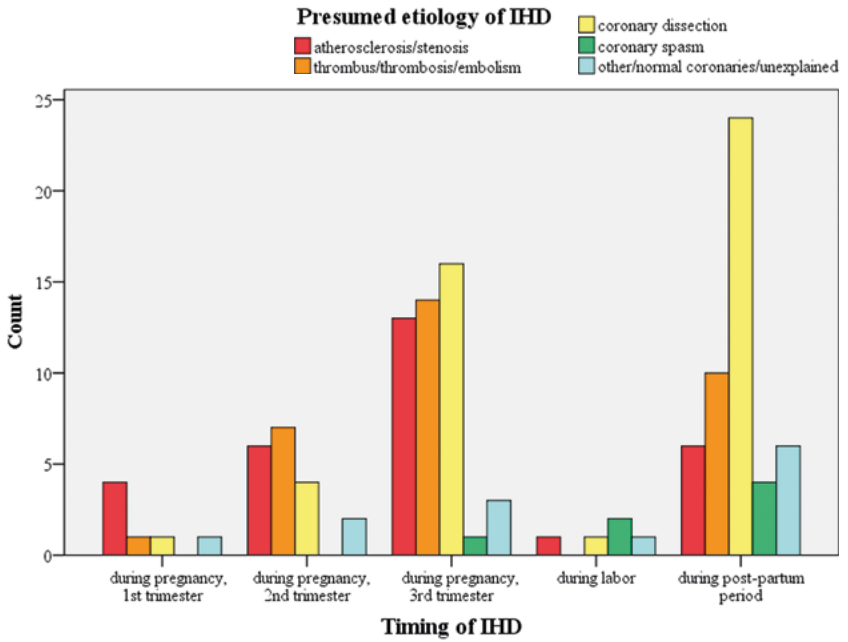

Figure 2. Aetiology of ischaemic heart disease depending on the time of presentation during pregnancy.

Table 1. Baseline characteristics of women with ischaemic heart disease presenting during pregnancy, according to the literature included in our review.

	N	Mean	SD
Pregnancies	146*		
Age of woman	145	33,2	5,8
Gravida	105	3,1	2,0
Parity	97	1,8	1,6
Coronary risk factors	**N (women)**		**Percentage**
Smoking	50		40
Dyslipidaemia	26		21
Pre-pregnancy hypertension	24		20
Family history	22		18
Obesity (pre-pregnancy BMI>30)	17		15
Diabetes Mellitus	9		8
Use of illegal drugs before event (cocaine)	3		3
One or more risk factors	80		63
Two or more risk factors	44		34
Cardiac history			
Chest pain	11		9
Valvular lesions	6		5
Heart failure	2		2
Supra ventricular tachycardia	2		2
Atrial fibrillation	2		2
Pulmonary embolus	1		1
Concurrent conditions			
Thyroid disease	4		3
Factor V Leiden	4		3
Thrombophillia	2		2
Connective tissue disease	2		2
Infectious disease	1		1
Other	19		12

Missing data were excluded for analysis. * including 6 twin-pregnancies and one triplet pregnancy.

Table 2. Overview and comparison of data described in the main literature concerning ischaemic heart disease during pregnancy and this study.

Literature (women)	Ladner et al. [5] (N=151)	Satoh et al. [17] (N=62)	James et al. [4] (N=859)	Roth et al. [6] (N=103)	This study *Overall* (N=146)	This study *Contemporary only* (N= 57)
Years of inclusion	1991-2000	1981-2001	2000-2002	1995-2005	1978-2012	**2005-2012**
Mean age of women (years)	31-35	33	33	33	33,2	33,5
Most common timing of coronary event (N)	Post-partum (62)	Post-partum (28)	During pregnancy, *not specified* (626)	During pregnancy, *not specified* (46)	During pregnancy, third trimester (56)	During pregnancy, third trimester (25)
Most common location of AMI (N)	*	Including anterior wall (31)	Including anterior wall (215)	Including anterior wall (73)	Including anterior wall (80)	Including anterior wall (26)
Most common aetiology of IHD (N)	*	Coronary dissection (14)	*	Coronary stenosis (41)	Coronary dissection (46)	Thrombus/ embolism (20)
Most common risk factor for IHD (N)	HT (*)	Smoking (9)	*	Smoking (46)	Smoking (40)	Smoking (17)
Maternal mortality (N)	7.3% (11)	3,2 % * (2)	5.1% (44)	11% (11)	8% (11)	6% (3)
Most common (other) maternal cardiac complication (N)	*	Cardiogenic shock (5), VF/VT (5), HF (5)	*	HF (9)	VT (17)	VT (3)
Most common maternal obstetric complication (N)	PIH (24)	PPH (1)	PPH (*)	Pre-eclampsia (6)	PIH (46)	PIH (6)
Cesarean section rate (N)	*	**	*	38% (39)	57% (75)	67% (36)
Perinatal mortality (N)	*	*	*	9% (6)	4% (5)	6% (3)
Most common offspring complication (N)	Prematurity (*)	Threatened premature delivery (3)	*	*	Prematurity (55)	Prematurity (28)

* = unknown or not clearly reported data, ** = at least 7 women, incompletely documented, AMI= acute myocardial infarction, HF= heart failure, HT= essential hypertension, IHD= ischaemic heart disease, PIH = pregnancy induced hypertensive disorders, including pre-eclampsia, eclampsia and Haemolysis Elevated Liver enzymes and Low Platelets (HELPP) syndrome, PPH = post-partum haemorrhage , VF= ventricular fibrillation, VT= ventricular tachycardia. Offspring mortality is defined as offspring death up to 20 weeks of gestation up to 7 days post-partum, prematurity is defined as age <37 wks. Missing data were excluded for analysis.

Table 3. Details of ischaemic heart disease and offspring outcomes in 146 pregnancies (including 6 twin-pregnancies and one triplet pregnancy) according to the literature included in our review. Missing data were excluded from analysis.

Presenting symptoms	N pregnancies	Percentage
Chest pain	131	95
Dyspnoea	38	36
Syncope	10	9
Dizziness	10	10
Heart failure syndrome	6	6
Palpitations	1	1
Exercise intolerance	4	4
No symptoms	0	0
Location of AMI		
Anterior, anteroseptal or anterolateral	80	67
Inferior, inferio-posterior or inferolateral	22	19
Other	13	14
Presumed etiology of IHD		
Coronary dissection	46	35
Thrombus/ embolism	33	25
Atherosclerosis/stenosis	31	24
Coronary spasm/other/ unexplained	20	15
Timing of AMI		
During pregnancy, 1st trimester	9	6
During pregnancy, 2nd trimester	22	15
During pregnancy, 3rd trimester	56	38
During post-partum period	50	33
During delivery	7	5
During pregnancy, unknown	2	1
Offspring outcome		
Live born	128	96
Perinatal death	5	4
Premature birth	55	56
Low birth weight	19	40
Small for gestational age	1	2
Apgar score (at 5 minutes)		
<7	5	16
7-10	27	84

AMI = acute myocardial infarction, perinatal death = intra uterine foetal death and stillborn. Premature birth is defined as <37 weeks, low birth weight is defined as, 2500 grams, small for gestational age is defined as <10 small for gestational age is defined as <10th percentile. Missing data were excluded for analysis.

Supplemental Table S1. Characteristics of included literature.

Authors	Year	Type of study
Aalders K., A. et al.[1]	1998	case series
Agostoni P. et al.[2]	2004	case report
Aliyary,S. et al.[3]	2007	case report
Allen,J.N. et al.[4]	1990	case report
Arimura T. et al.[5]	2009	case report
Ascarelli,M.H. et al.[6]	1996	case report
Babic,Z. et al.[7]	2011	case report
Badui,E. et al.[8]	1994	case series
Balmain,S. et al.[9]	1997	case report
Baskurt,M. et al.[10]	2012	case report
Bauer,M.E. et al.[11]	2012	case report
Beary,J.F. et al.[12]	1979	case series and review
Bornstein,A. et al.[13]	1984	case report
Boyer,W.B. et al.[14]	2011	case report
Boztosun,B. et al.[15]	2008	case report
Brahim,Y.B. et al.[16]	2008	case report
Brandenburg,V.M. et al.[17]	2004	case report
Bucciarelli,E. et al.[18]	1998	case report
Chabrot,P. et al.[19]	2009	case report
Chant,G.N.[20]	1979	case series and review
Chen,Y.C. et al.[21]	2009	case report
Cohen,W.R. et al.[22]	1983	case report
Collins,J.S. et al.[23]	2002	case report and review
Collyer,M. et al.[24]	2004	case report
Cowan,N.C. et al.[25]	1988	case report
Craig,S. et al.[26]	1999	case report
Cuthill,J.A. et al.[27]	2005	case report and review
Dhawan,R. et al.[28]	2011	case report
Dhawan,R. et al.[29]	2002	case report
Diessner,J. et al.[30]	2011	case report
Dwyer,B.K. et al.[31]	2005	case report
Ehya,H. et al.[32]	1980	case report
Eickman,F.M.[33]	1996	case report
Elming,H. et al.[34]	1999	case report and review
Emori,T. et al.[35]	1993	case report
Eom,M. et al.[36]	2005	case report
Eriksson,U. et al.[37]	1999	case report
Esinler,I. et al.[38]	2003	case report
Fayomi,O. et al.[39]	2007	case report
Frey,B.W. et al.[40]	2006	case report
Garry,D. et al.[41]	1996	case report
Garvey,P. et al.[42]	1998	case report
Ginwalla,M. et al.[43]	2010	case report
Giudici,M.C. et al.[44]	1989	case report
Hamada,S. et al.[45]	1996	case report
Hameed,A.B. et al.[46]	2000	case series
Hands,M.E. et al.[47]	1990	case series
Hankins,G.D. et al.[48]	1985	case series and review
Hoppe,U.C. et al.[49]	1998	case report
Houck,P.D. et al.[50]	2012	case report
Iaccarino,D. et al.[51]	2010	case report
Iadanza,A. et al.[52]	2007	case report and review
Janion,M. et al.[53]	2007	case series
Jimenez Valero.S. et al.[54]	2005	case series
Jungbluth,A. et al.[55]	1988	case report
Kamran,M. et al.[56]	2004	case report
Kearney,P. et al.[57]	1993	case series and review
Klutstein,M.W. et al.[58]	1997	case series
Knoess,M. et al.[59]	2007	case series
Koul,A.K. et al.[60]	2001	case series and review
Kuczkowski,K.M.[61]	2005	case report
Kulka,P.J. et al.[62]	2000	case report
Kurum,T. et al.[63]	2003	case report
Laudanski,K. et al.[64]	2011	case report and review

Laudanski,K. et al.[64]	2011	case report and review
Lerakis,S. et al.[65]	2001	case report
Liu,S.S. et al.[66]	1992	case report
Livingston,J.C. et al.[67]	2000	case report
Mabie,W.C. et al.[68]	1988	case report
Madu,E.C. et al.[69]	1994	case report and review
Maeder,M. et al.[70]	2005	case report and review
Majdan,J.F. et al.[71]	1983	case report
Mak,K.H. et al.[72]	2004	case report
Makkonen,M. et al.[73]	1995	case report
Marcoff,L. et al.[74]	2010	case report
Martins,R.P. et al.[75]	2010	case report
McAdams,S.A. et al.[76]	1986	case series
McHugh,M.J. et al.[77]	1990	case report and review
McKechnie,R.S. et al.[78]	2001	case report
McKeon,V.A. et al.[79]	1989	case report and review
Moore,A.D. et al.[80]	2012	case report
Movsesian,M.A. et al.[81]	1989	case report
Nabatian,S. et al.[82]	2005	case series
Nallamothu,B.K. et al.[83]	2005	other
Newell,C.P. et al.[84]	2011	case report
O'Donnell,M. et al.[85]	1987	case report
Oki,K.N. et al.[86]	2011	case report
Ottman,E.H. et al.[87]	1993	case report
Pauleta,J.R. et al.[88]	2007	case report
Phillips,L.M. et al.[89]	2006	case report
Pierre-Louis,B. et al.[90]	2008	case report and review
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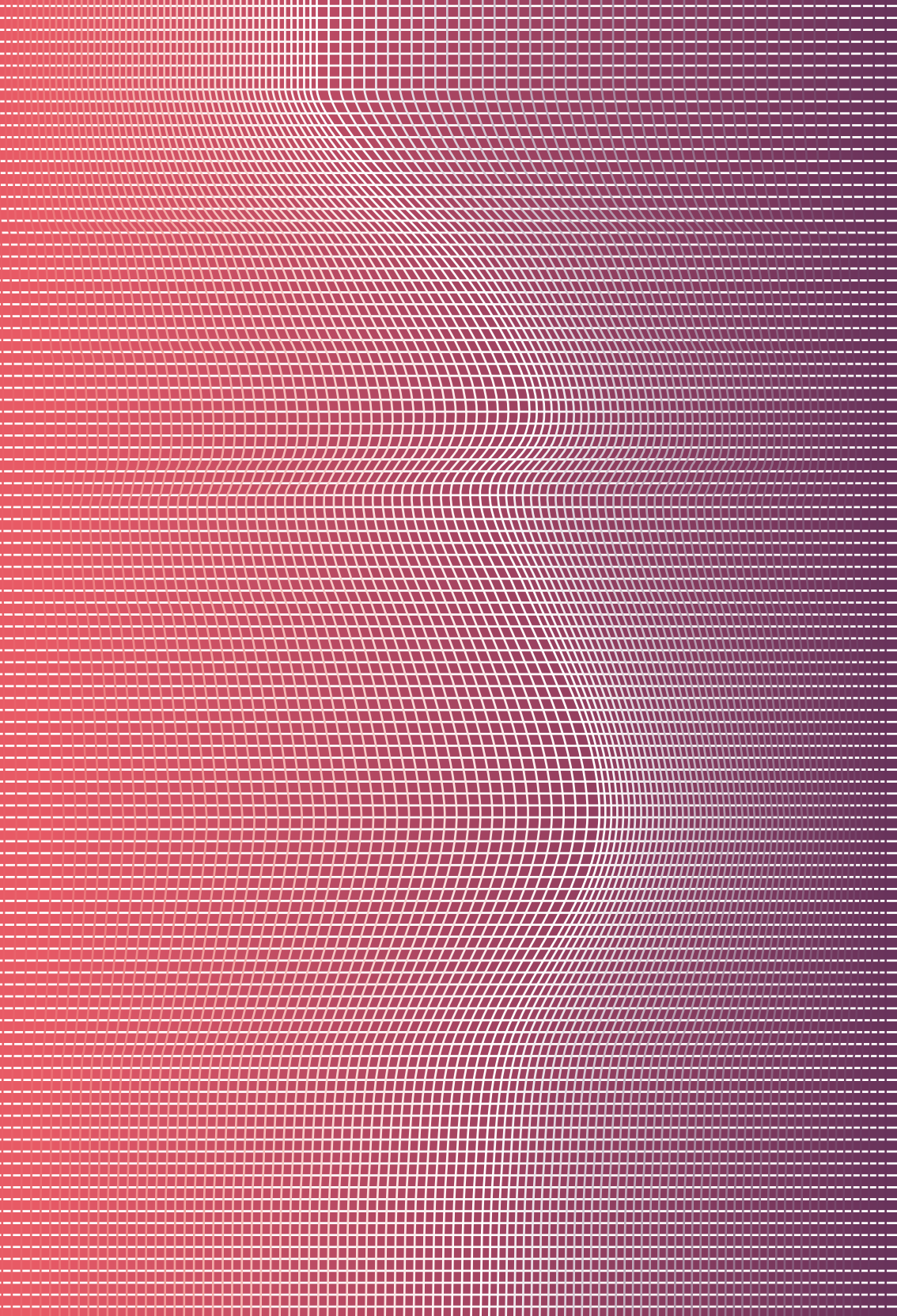

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Pregnancy related myocardial infarction

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Neth Heart J. 2017 Jun;25(6):365-369. doi: 10.1007/s12471-017-0989-9.

ABSTRACT

Introduction

The risk of acute myocardial infarction in young women is low, but increases during pregnancy due to the physiological changes in pregnancy, including hypercoagulability. Ischaemic heart disease during pregnancy is not only associated with increased maternal morbidity and mortality, but also with high neonatal complications. Advancing maternal age and other risk factors for cardiovascular diseases may further increase the risk of ischaemic heart disease in young women.

Methods

We searched the coronary angiography database of a Dutch teaching hospital to identify women with acute myocardial infarction who presented during pregnancy or postpartum between 2011 and 2013.

Results

We found two cases. Both women were in their early thirties and both suffered from myocardial infarction in the postpartum period. Acute myocardial infarction was due to coronary stenotic occlusion in one patient and due to coronary artery dissection in the other patient. Coronary artery dissection is a relatively frequent cause of myocardial infarction during pregnancy. Both women were treated by percutaneous coronary intervention and survived.

Conclusion

Physicians should be aware of the increased risk of myocardial infarction when encountering pregnant or postpartum women presenting with chest pain.

INTRODUCTION

Ischemic heart disease (IHD) and acute myocardial infarction (AMI) in fertile women is rare.[1] However, pregnancy greatly increases the risk for IHD in these women.[2 3] This is explained by the physiological changes of pregnancy, including a hyperdynamic circulation and hypercoagulability. An ongoing increase in maternal age and other risk factors for cardiovascular diseases may further increase the risk of IHD in young women.[4 5] IHD during pregnancy is not only related with increased maternal morbidity and mortality, but also high offspring complications.[2 6 7] Information about IHD during pregnancy or the post- partum period is scarcely available and mainly consists of case reports, two studies, and few reviews.[2 6-9] While the treatment of IHD advances, contemporary cases of pregnancy related IHD are scarce.[7] We therefore present two recent cases of AMI presenting during pregnancy or in the postpartum period .

METHODS

We searched the coronary angiography (CAG) database of the department of cardiology of the Medical Centre Leeuwarden, Leeuwarden, a teaching hospital in the Netherlands. Fertile women (defined as <45 years) who underwent CAG between March 2011 and March 2013 were selected. Women who underwent CAG during pregnancy or up to 3 months post-partum were included We searched their medical files for proven IHD, coronary artery disease (CAD) or AMI, based on CAG results during pregnancy and up to three months post-partum..

REPORT

Fourteen young, fertile women underwent CAG. Two women met our inclusion criteria.

Case 1

A 31 year old woman, gravida 8 para 4 (G8P4), was seen at our cardiology department with chest pain. She had delivered a healthy new born three weeks before. Furthermore, she had a history of alcohol and illicit substance abuse (cocaine and amphetamine). Other risk factors for cardiovascular diseases were smoking, hypertension and hypercholesterolemia. She presented with chest pain, and additionally she complained about nausea, vomiting, excessive transpiration and epigastric pain. Physical examination showed a pale woman with a damp skin. She was hypotensive (blood pressure 87/53 mmHg) with a heart rate of 60 beats per minutes. Cardiac auscultation was unremarkable. ECG showed acute ST-elevation myocardial infarction (STEMI) (figure 1). Echocardiography showed

a moderately reduced left ventricular function with akinesis of the septal, anterior and distal inferior wall, without signs of pericardial effusion. A CAG was performed, see figure 2. She was treated with bare metal stenting. Creatin Kinase (CK) levels raised to 3760, CK-MB levels to 217. A toxicology screening was performed at presentation and she tested negative for cocaine or other illicit drugs. She was discharged after five days in a stable condition. During follow up she was admitted to a cardiac revalidation program and was encouraged to alter her high-risk lifestyle. Echocardiography during follow up showed an estimated left ventricular ejection fraction of 40-45%.

Case 2

A 30 year old woman, G3P3, with a history of migraine headaches for which she incidentally used tramadol and acetaminophen, was seen 3 months postpartum in our emergency department. She complained about chest pain and excessive transpiration. Pain diminished after administration of nitroglycerine sublingually. Physical examination revealed that she was in shock, she had a systolic blood pressure of 90 mmHg and a regular tachycardia of 120 beats per minute. Furthermore, she had a pale, cold skin. Auscultation revealed no cardiac murmurs. ECG suggested ST elevation anterior wall infarction. CAG was performed and revealed an occlusion of the left main coronary artery and a dissection of the LAD and circumflex coronary artery (figure 3). During CAG external defibrillation was applied twice for ventricular fibrillation. Echocardiography after the CAG showed akinesis of the anterior wall and mitral valve regurgitation grade II. Because of her compromised hemodynamic state despite the initiation of inotropics, an intra-aortic balloon pump was inserted. Emergency coronary artery bypass grafting (CABG) was performed with a left internal mammary artery (LIMA) graft to the LAD and a saphenous venous graft to the anterolateral and margo obtusus branches. A subsequent postoperative cardiogenic shock was treated with the intra-aortic balloon pump during one day and with inotropics, continued for two days. Her condition improved steadily and she could be discharged from the intensive care unit after five days. At hospital discharge, ten days after admission, echocardiography showed a moderately reduced left ventricular function without valvular regurgitation. At follow up 3 weeks after discharge she was in stable condition without signs or symptoms of ischemia or heart failure.

DISCUSSION

We identified two cases of pregnancy related IHD in a teaching hospital over a 2 year period of time. As previously described in this journal, pregnancy-related IHD is rare, with an incidence of 2.8 to 6.2 per 100.000 deliveries described in recent reviews.[2 3 6] In this large teaching hospital only 14 women of fertile

age underwent a CAG during the period searched, and 2 of them (14%) had pregnancy-related IHD. One of our patients had several risk factors for IHD, similar to the literature where a high prevalence of risk factors is reported in pregnancy-associated IHD, specifically when atherosclerotic disease is present.[7] Our second patient who had a coronary artery dissection however had no risk factors for CAD, which is again consistent with current literature.[7] Coronary artery dissection, which is rare outside pregnancy, is one of the main aetiologies of AMI during pregnancy or the post-partum period.[7]

Both women presented with chest pain in the postpartum period. This is consistent with the literature, where most cases of AMI during pregnancy present with chest pain, during the 3rd trimester or the postpartum period, and mostly comprise the anterior myocardial wall.[2 3 6]

Both women were successfully treated for IHD and survived. Myocardial infarction presenting during or shortly after pregnancy is a very high risk condition with maternal mortality rates ranging 5.1 to 11%.[2 3 6] When a pregnant woman presents with chest pain, the diagnoses to be considered are pulmonary embolism, aortic dissection and myocardial infarction. ECG and Troponin levels should be assessed to diagnose infarction, while echocardiography and CT scan are important to diagnose aortic dissection and pulmonary embolism. In women with a STEMI and in women with a non-STEMI who have risk factors, the preferred treatment is PCI according to current guidelines.[8] Bare metal stents are preferred over drug-eluting stents in pregnant women, because prolonged dual antiplatelet therapy is preferably avoided.[8 9] In stable patients with coronary artery dissection a more conservative approach has been advocated, since spontaneous healing often occurs while PCI is frauded by technical difficulties and a high failure rate.[10] Medical treatment can include beta-blockers and acetylsalicylic acid. Clopidogrel, though being safe in animal studies, should be used with caution since experience in humans is limited. ACE- inhibitors and Angiotensin receptor blockers are contra-indicated during pregnancy. Vaginal delivery is usually appropriate.[11] In follow-up, next to common IHD risk factor management such as reducing smoking habits, obesity, hypertension, hypercholesterolemia or lipoprotein disorders, anti-phospholipid syndrome as a contributor to myocardial infarction in young women with a history of pregnancy morbidity such as spontaneous abortions, as observed in our first case, should be evaluated.[12]

CONCLUSION

Physicians should be aware of this increased risk of manifestations of IHD when encountering young, pregnant or postpartum women with chest pain.

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FIGURES

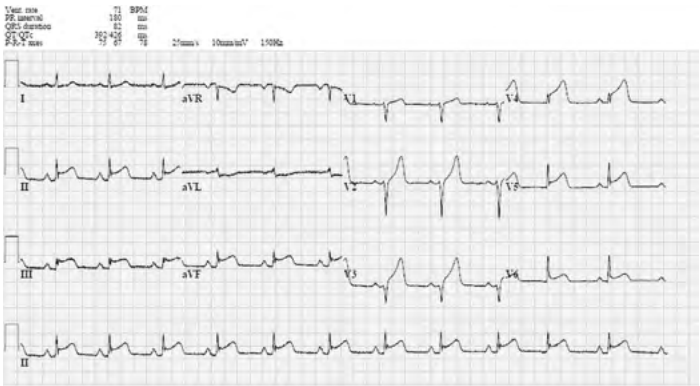


Figure 1. An ECG showing ST segment elevation in leads II, III, aVF and V2–V5 and minimal ST segment depression in aVL, suggesting panischaemia.

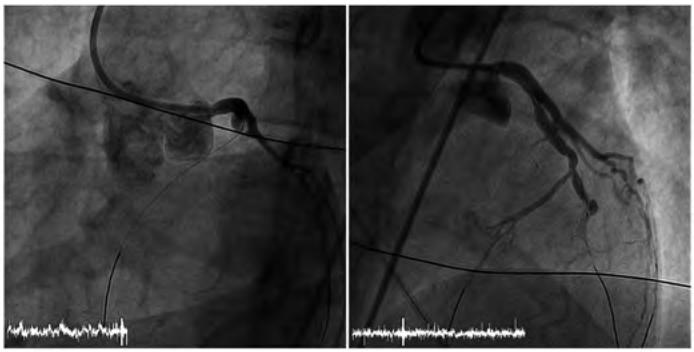


Figure 2. A coronary angiography of patient 1, showing occlusion of the left anterior descending artery distally from the first diagonal artery before and after treatment.

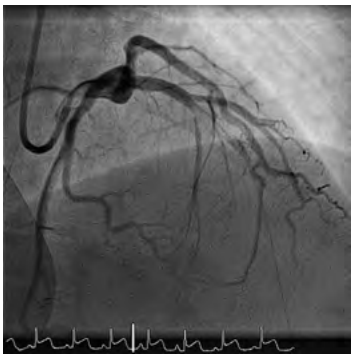
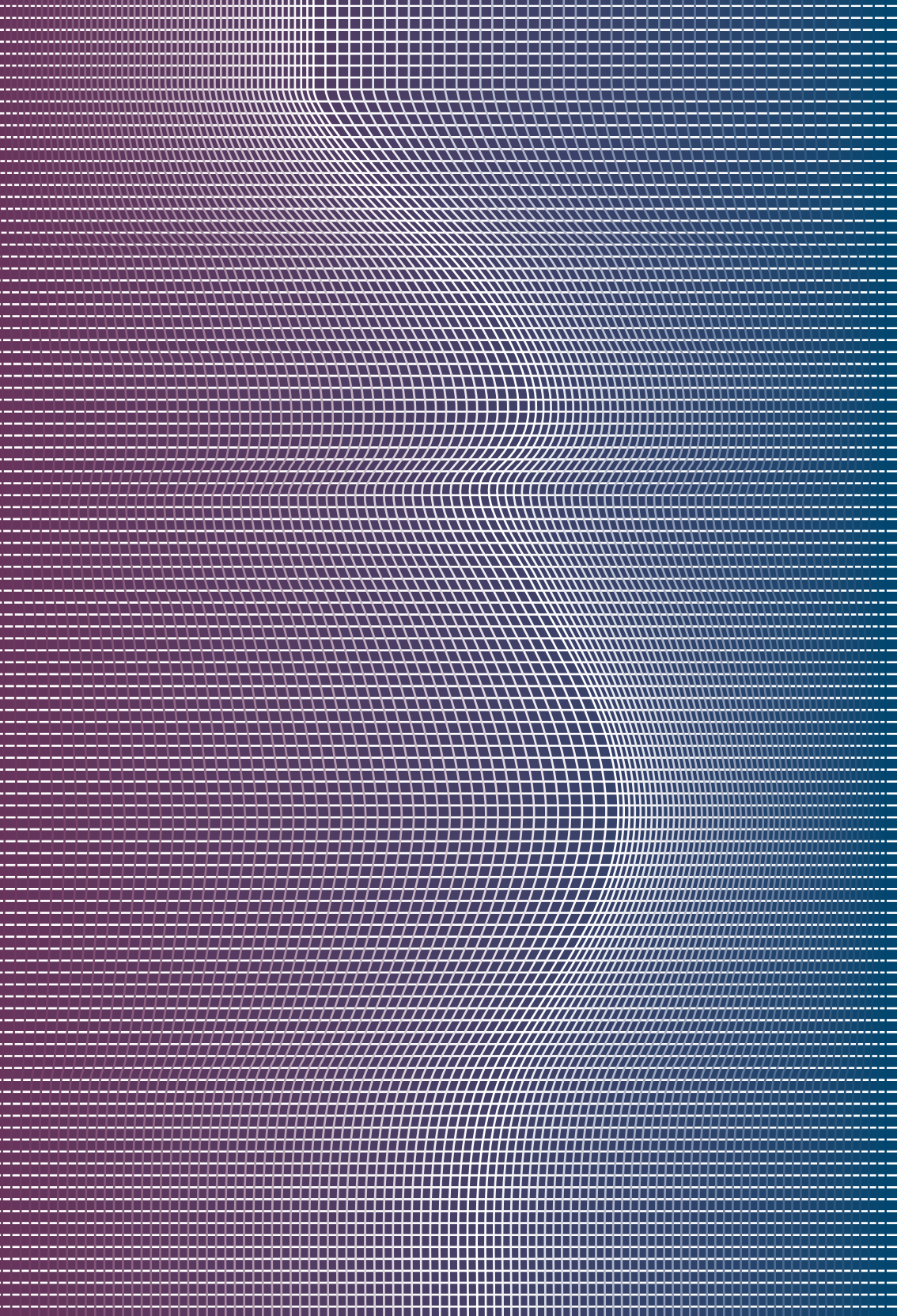


Figure 3. A coronary angiography of patient 2, showing an occlusion of the left main coronary artery and a dissection of the left anterior descending artery and circumflex coronary artery.



5

Pregnancy in women with pre-existent ischemic heart disease; a systematic review with individualized patient data

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ABSTRACT

Introduction

Studies on pregnancy risk in women with ischemic heart disease (IHD) have mainly excluded pregnancies in women with pre-existent IHD. There is a need for better information about the pregnancy risks in these women and their offspring.

Methods

We performed a systematic review searching the Pubmed/Medline public database for pregnancy in women with pre-existent IHD analysing the cardiac, obstetric and foetal/neonatal outcome of pregnancy in women with pre-existing IHD. Individual patient data were requested from large series. The primary outcome endpoints was a composite of ischemic complications including maternal death, acute coronary syndrome and ventricular tachycardia.

Results

116 women with pre-existent IHD had 124 pregnancies including 1 twin pregnancy. These women had a 21% chance of having an uncomplicated pregnancy (completed pregnancy without cardiovascular, obstetric or foetal/neonatal complications, n=26). Primary outcome endpoints occurred in 25% of the pregnancies (n=29), and were more frequent where atherosclerosis was the underlying pathology for IHD (45% versus 14% of the pregnancies with other underlying pathology, p=.005). There were two maternal cardiac deaths (2%), one of which one occurred in the 18th week of pregnancy. Obstetric complications occurred in 58% (n=65) of pregnancies and feta/neonatal complications in 42% (n=47).

Conclusion

Pregnancies in women with pre-existing IHD are high risk pregnancies. These women have a high risk of ischemic cardiovascular complications including maternal mortality. The risk of ischemic complications is especially high among women with atherosclerotic coronary artery disease.

INTRODUCTION

It is expected that more women with pre-existing ischemic heart disease (IHD) will become pregnant, due to increasing maternal age and an increasing incidence of traditional risk factors for IHD in pregnant women.[1 2] IHD highly contributes to maternal mortality due to cardiovascular disease, which is the number one cause for indirect maternal mortality in the developed world.[3]

Studies on pregnancy risk in women with IHD have mainly focused on acute presentation and management of ischemic events, and excluded pregnancies in women with pre-existent IHD.[4 5] The largest study to date of pregnancy in women with pre-existing IHD reported an increased complication risk with significant adverse maternal cardiac events occurring in 10%. The small sample size of this study,[6] combined with a general scarcity of research in this area, means that many clinicians remain uncertain about the risk of pregnancy in women with pre-existent IHD. To address this knowledge gap we performed a systematic review analysing the cardiac, obstetric and foetal/neonatal outcome and complications of pregnancy in women with pre-existing IHD.

METHODS

We used the PRISMA-statement protocol and searched the *MedLine public database* for all studies dated until 13-07-2017.[7] Search terminology was; ("Myocardial Ischemia"[Mesh]) AND "Pregnancy"[Mesh], Myocardial Ischemia AND Pregnancy, coronary artery disease AND Pregnancy, Ischemic heart disease AND Pregnancy, acute coronary syndrome AND Pregnancy, myocardial infarction AND Pregnancy. The filters Humans, English, German, Dutch, Female, Adolescent: 13-18 years and Adult: 19+ years were activated. We only included studies written in English, German and Dutch to reduce misinterpretation of data. Exact duplicates were removed electronically. We included all online available articles, either from open access publishing and availability provided by the University Medical Centre Groningen. Articles that were not available for the University Medical Centre Groningen were bought. Articles not describing ischemic heart disease in relation to pregnancy, only describing myocardial ischaemia during pregnancy, or ischemic heart disease caused by Kawasaki or Takayasu disease were excluded. For studies describing >6 patients the authors were contacted to provide individual patient data. Smaller series or cases were only included when sufficient individual patient outcome data were described. The search and exclusion procedure was performed twice by the principal investigator (HL).

Collected data

Collected baseline date were maternal age at timing of diagnosis of ischemic heart disease and at gestation, coronary artery disease aetiology, coronary interventions (including thrombolysis, percutaneous coronary intervention, PCI, and coronary artery bypass crafting, CABG), pre-pregnancy occurrence of angina pectoris (AP) or acute myocardial infarction (AMI, specified as ST-elevation myocardial infarction (STEMI) and non ST-elevation myocardial infarction, NSTEMI), smoking history, comorbidities (diabetes, obesity, hypertension, inherited thrombophilia, connective tissue disease, other heart disease, dyslipidaemia and other manifestations of vascular thrombosis such as deep venous thrombosis (DVT), pulmonary embolism (PE) or cerebrovascular event (CVA)), New York Heart Association (NYHA) functional class, pre- pregnancy medication and left ventricular systolic function (defined as: normal function (left ventricular ejection fraction, LVEF≥55%), mild (45%–54%), moderate (30%–44%) or severe (<30%) systolic dysfunction).

Our primary endpoints were ischemic cardiovascular events including cardiac arrest or cardiac death, ventricular tachycardia (VT) needing treatment and/or hospitalisation or recurrence of coronary ischemic events (including angina pectoris and acute coronary syndrome).

Secondary endpoints were divided in secondary cardiovascular, obstetric, and foetal/neonatal complications. Secondary cardiovascular complications were other cardiac arrhythmias (not VT fulfilling the criteria of primary endpoint), heart failure, other thrombotic events (deep venous thrombosis, DVT, pulmonary embolism, PE, or cerebrovascular event, CVA), new onset heart valve disease and endocarditis. Obstetric complications were Caesarean section (CS, planned and emergency), pregnancy induced hypertension (PIH), (pre)eclampsia, haemolysis elevated liver enzymes low platelet (HELLP) syndrome and postpartum haemorrhage (as reported a blood loss >500 mL after vaginal delivery or >1000 mL after CS or need for transfusion therapy) and gestational diabetes.

Completed pregnancies were defined as pregnancies beyond >24 weeks duration. Incompleted pregnancies were subdivided in spontaneous and elective abortions. Foetal/neonatal complications were defined as foetal/neonatal death (death after ≥24 weeks of gestation up to 28 days postpartum), late neonatal death (28 days post-partum up to 1 year post-partum), neonatal respiratory distress syndrome, neonatal intensive care unit (NICU) admission, premature birth (birth <37 weeks gestation), low birth weight (birth weight <2500 grams), small for gestational age (as documented in case reports or as reported by the treating physician in larger studies) and occurrence of congenital (heart) disease in the offspring.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics Premium' V 22 for Windows (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, version 22.0. Armonk, NY: IBM Corp.) Missing data were excluded for analysis. Continuous data are presented as a mean with a standard deviation (SD) or a median with an interquartile range (IQR) or range, depending on their distribution. Normality was tested with the Kolmogorov-Smirnov test with Lilliefors' correction. Absolute numbers and percentages were presented for categorical data. We used the Chi-square test for comparison of categorical variables, the independent t-test for comparison of two means. A $p \leq .05$ was considered statistically significant, all tests are two-tailed.

RESULTS

We included 37 articles describing 124 pregnancies (including 1 twin pregnancy) in 116 women with IHD, published between 1956 and 2015 (see figure 1 and table 1). Next to individual data extracted from case reports, individual patient data from 2 larger studies were requested and obtained, see table 1. Baseline data and use of medication for the women who became pregnant after diagnosis of IHD are described in table 2. Seven women had two pregnancies and one woman three pregnancies after IHD diagnosis.

Primary endpoints and secondary cardiovascular complications

Primary (ischemic) endpoints occurred in 25% of pregnancies, as displayed in table 3. For the sub-set of pregnancies in women with atherosclerosis as the underlying pathology for IHD, primary endpoints occurred in 45% versus 14% of pregnancies in women with other underlying pathology for IHD (p=.005). Pre-pregnancy revascularisation therapy (PCI, CABG or thrombolysis) did not influence primary endpoint outcome (27% occurrence of primary outcome endpoint occurrence in pregnancies with revascularisation therapy versus 24% in pregnancies without, p=.75), neither did NYHA classification prior to pregnancy (33% occurrence of primary outcome endpoint occurrence in pregnancies in women with NYHA functional class 2-4 versus 21% of the pregnancies in women with NYHA class 1, p=.34) or LVEF <45% (20% of the women with LVEF <45%, versus 30% in women with LVEF ≥45%, p=.53), nor maternal age.

Overall, there were two maternal deaths (2%). One 41-year old woman with medically treated IHD and NYHA class III died in the 18th week of pregnancy due to cardiac arrest after re-infarction, 4 years after her first AMI. A 27-year old woman who received a diagnosis of coronary spasm 5 years prior to pregnancy, for which she did not receive therapy, died suddenly 2 months post-partum after an uncomplicated pregnancy. Unstable angina occurred in two women, both during

pregnancy. Non-ST elevation myocardial infarction occurred in 8 pregnancies, 4 of which occurred in the post-partum period. Primary endpoints occurred in 25% of pregnancies in women who were multiparous (n=19) compared to 27% (n=8) pregnancies in nulliparous women (p=.83). Two out of ten (20%) women with pre-pregnancy coronary dissection had recurrence of coronary dissection. For details of the pregnancies complicated by acute coronary syndrome, see table 4.

Women who did not use anticoagulation therapy during pregnancy (low molecular weight heparins, LMWH, unfractioned heparins, UFH or vitamin K antagonists, VKA) did not have a higher occurrence of primary endpoints than women who did use anticoagulation therapy (22% versus 27%, p=.56). Women who did use neither anticoagulation therapy nor platelet inhibition did not have more primary endpoints than women who did use one of these therapies (19% in women without vs 27% in women with use of anticoagulation and or antiplatelet therapy, p=.36)

Secondary cardiovascular complications are displayed in table 3. Pulmonary embolism occurred during one pregnancy in the 1st post-partum week and occurred combined with hepatic artery thrombosis, spleen infarction and multiple arterial dissections in a woman who was not known to have connective tissue disease.

Obstetric and foetal/neonatal complications

Incompleted pregnancies

There were 12 incompleted pregnancies, of which 10 spontaneous abortions, 1 early intra uterine foetal death due to maternal death, and 1 elective termination. Two of the incompleted pregnancies were associated with maternal cardiovascular complications: one was related to maternal death, the other to recurrent unstable AP and CABG. The elective termination had a maternal cardiac indication: recurrent AMI and PCI.

Completed pregnancies

Obstetric complications are displayed in table 5 and occurred in 58% of the pregnancies (n=65). Excluding planned caesarean section (CS), 34% of the women had obstetric complications (n=38).

Planned CS was performed for maternal indication in 12 women (33%, PIH n=3 pre-eclampsia n=4, ischemic complication n=5).

Fifty percent of the planned CS resulted in premature delivery versus 22% of prematurity with delivery of other modalities (including vaginal delivery and emergency CS, p=.003, missing data n=2). Planned CS with delivery of a premature neonate was performed for maternal indication in 5 pregnancies (29%, PIH (n=2), pre-eclampsia (n=2) and cardiac ischemia), other indications are unknown.

Foetal/neonatal complications occurred in 42% of the neonates, of which 15% (n=17 neonates) were related to planned CS. For details, see table 6. Low birth weight was reported in 45% of neonates delivered through planned CS, versus 18% of the neonates who were delivered by other modalities (including vaginal delivery and emergency CS, p=.006). Maternal use of beta-blockers during pregnancy was unrelated to neonatal LBW (31% LBW in pregnancies with beta-blocker use vs 25% without, p=.59)

Neonatal death occurred in 4 neonates (4 %). One neonatal death occurred in a 37 year old woman whose pregnancy was complicated by PIH and a STEMI, she delivered a stillborn at 37 weeks. Another 47 year old woman without cardiovascular complications during pregnancy delivered a lifeless neonate with a VSD and trisomy 18 at 30 weeks of pregnancy. The other two neonates died after uncomplicated pregnancies due to unknown cause. A late neonatal death occurred once, in a 47 year old woman whose pregnancy was complicated by PIH. She delivered a premature LBW neonate at 30 weeks with trisomy 18 who died 40 days after delivery. During her pregnancy maternal ACE-inhibitor use was reported.

In addition to the 2 neonates who died with congenital disease, 5 other neonates had a congenital disease including ASD (needing surgical correction), VSD, trisomy 21, caroli disease (congenital cystic dilatation of the intrahepatic bile ducts) and an unspecified congenital disease, all unrelated to maternal VKA, ACE-inhibitor or statin use.

Any adverse outcomes

Overall the chances of having an uncomplicated pregnancy (completed pregnancy without cardiovascular, obstetric or foetal/neonatal complications was 21% (n=26). When excluding complications related to planned CS the chances of having an uncomplicated pregnancy (completed pregnancy without cardiovascular, obstetric or foetal/neonatal complications) was 38% (n=47).

DISCUSSION

Our systematic review highlights the high risk nature of pregnancies in women with pre-existing IHD. Women have a 1 out of 4 chance of ischemic cardiovascular complications including maternal mortality in 2%. Women with atherosclerotic disease as underlying pathology appear at especially high risk for ischemic complications, both during pregnancy and the post-partum period. The re-occurrence rate of acute coronary syndrome in women with IHD is high occurring in 1 out of 11 (10%) of pregnancies. Women with coronary dissection as the underlying pathology have an especially high (1 out of 5) risk of re-dissection.

While new onset IHD during pregnancy and serious cardiovascular complications mainly occurs at the end of pregnancy or the post-partum period,[4] maternal ischemic complications in women with pre-existent IHD are not limited to late pregnancy, as demonstrated by serious maternal cardiovascular morbidity including maternal death in 2 out of 12 incompleted (early) pregnancies. Clearly, pregnancies in these women should be classified as high risk pregnancies (modified WHO class of maternal risk of cardiovascular complications III).[10-12] This is underlined by another recently published risk score, the CARPREG II score, which adapted coronary artery disease as a lesion specific predictor for cardiac complications during pregnancy.[13]

In addition to serious ischemic cardiovascular complications, pregnant women with IHD appeared at high risk of obstetric complications, occurring in 58% of the cases. Planned CS significantly contributed to obstetric as well as foetal/neonatal complications including prematurity and LBW. However, a significant limitation is the Current European guidelines suggest a vaginal delivery in most women with heart disease, and advocate the use of CS for obstetric indications.[14] Planned CS is considered for women with several cardiovascular diseases (aortic, heart failure) and for women who are anticoagulated on warfarin at the time of labour.[14] The high incidence of planned CS in this study (32%) may be explained by the preference of the leading physician, preferring controlled circumstances in an operation room may hypothetically be preferential.[14] Furthermore, some may be repeat CS. Also, not all cases are European in origin, and the higher incidence of planned CS even in the healthy population of women in the United States (33%) may raise the ratio of planned CS in this study (as many cases were northern American origin).[15] However, as a concerning fact, planned CS led to preterm birth in 17 neonates of which 1 died after delivery (probably related to trisomy 18). In only 5 of these cases the choice for preterm planned CS delivery is explained by maternal indication due to pregnancy morbidity. Possibly, due to missing data, the maternal indication for these other planned CS was unknown. Another explanation for the premature CS deliveries may be physicians' unfamiliarity regarding the pregnancy and delivery risk in women with IHD.

LBW was suggested to be related to beta-blocker use in recent literature, which we could not confirm in our population of women with pre-existent IHD.[16] However, possibly the sample size was too small to detect any difference. The high incidence of congenital anomalies (6%) remains unexplained; none of the mothers had congenital (heart) disease, and the incidence was unrelated to the use of known foetotoxic medication during pregnancy.

Our review indicates a high risk of cardiac as well as of obstetric and foetal/neonatal complications in women with pre-existent IHD. Pre-pregnancy evaluation and counselling of these women is mandatory. From early pregnancy

on these women should be managed as high-risk pregnancies according to guidelines, by experts in pregnancy and heart disease and antenatal care should include frequent clinical assessment with focus on early detection of myocardial ischemia. Monitoring should continue during the post-partum period.

LIMITATIONS

Our study was limited by scarcity of literature, missing data related to study design and reporting bias due to inclusion of case reports. Furthermore, a significant amount of included studies were not recent which may have biased or influenced outcomes by dated treatment options. Inherent bias may be present because possibly many women with (suspected high risk) coronary artery disease (including women with coronary dissections due to connective tissue disease) may have been advised against pregnancy. Therefore the risk of pregnancy in women with ischemic heart disease may be even higher than reflected in our study.

CONCLUSIONS

Pregnancies in women with pre-existing IHD are high risk pregnancies with a 1 in 4 chance of serious cardiovascular complications including maternal mortality. Women with atherosclerotic coronary disease as underlying pathology appear at highest risk for ischemic complications. The chances of an uncomplicated pregnancy are low (21%) highlighting the need for very close maternal and foetal surveillance during pregnancy.

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TABLES AND FIGURES

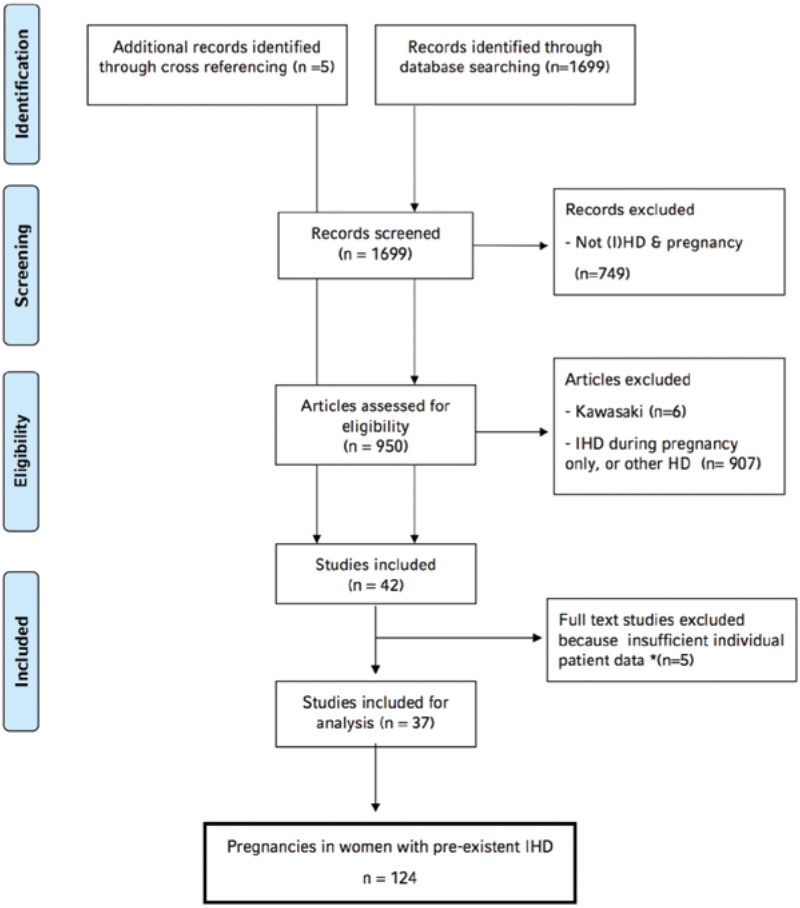


Figure 1. Inclusion.[7] IHD = Ischemic heart disease. HD = heart disease. * of ≤6 patients, for studies describing >6 patients (n=2) the authors provided individual patient data.

Table 1. Included studies.

Author	Year of publication	Study type	Pregnancies (N)
Aalders,K. et al.[17]	1998	retrospective case series	2
Abramovitz,S.E. and Beilin,Y.[18]	1999	case report	1
Bagg,W. et al.[19]	1999	retrospective case series	2
Chestnut,D.H. et al.[20]	1986	case report	1
Darias,R. et al.[21]	2001	case report	1
Dawson,P.J. et al.[22]	1988	case report	1
De Santis,M. et al.[23]	2011	case report	1
Dufour,P. et al.[24]	1997	case report	1
Dufour,P.H. et al.[25]	1997	case report	1
Frenkel,Y. et al.[26]	1991	retrospective case series	4
Gast,M.J.and Rigg,L.A.[27]	1985	retrospective case series	3
Glaser,D. et al.[28]	1988	case report	1
Gordon,S.[29]	1988	case report	1
Guven,S. et al.[30]	2004	case report	1
Hackney,D.N. et al.[31]	2007	case report	1
Honig,O. et al.[32]	1998	case report	1
Klinzing,P. et al.[33]	2001	case report	2
Nakajima,Y. et al.[34]	2011	case report	1
Ohkuchi,A. et al.[35]	2009	case report	1
Pombar,X. et al.[36]	1995	case report	1
Radio,G.J. and Chefetz,M.D.[37]	1978	case report	1
Reece,E.A. et al.[38]	1986	case report	1
Rhen,K. and Salokannel,J.[39]	1967	case report	1
Rosenlund,R.C. an Marx,G.F.[40]	1988	case report	1
Siegler,A.M. et al.[41]	1956	case report	1
Silfen,S.L. et al.[42]	1980	case report	1
Smith,R.L. et al.[43]	2008	retrospective case series	5
Tedoldi,C.L. and Manfroi,W.C.[44]	2000	case report	1
Tello-Montoliu,A. et al.[45]	2013	case report	1
Tweet,M.S. et al.[46]	2015	retrospective case series	8
Velasco,J.G. et al.[47]	1994	case report	1
Verbruggen,M. et al.[48]	2015	case report	1
Vinatier,D. et al.[49]	1994	case report	1
Wender-Ozegowska,E. et al.[50]	2012	case report	1
Wilson,A.M. et al.[51]	2004	case report	1
Roos-Hesselink,J.W. et al.[11]	**2013**	**combined retrospective and prospective registry**	**20**
Burchill,L.J. et al.[6]	**2015**	**retrospective cohort study**	**50**

When ≥3 authors only the first author was mentioned followed by 'et al.'. Studies for which individual patient data were separately collected are represented in bold font.

Table 2. Baseline data and use of medication for women who became pregnant after manifestations of IHD. Missing data were excluded for analysis.

	All cases (N,%)	Missing data (N)
Pregnancies	125	
Women	**116**	
Mean age at diagnosis IHD (mean years, [SD])	30.8 [5.9]	55
Mean time between diagnosis of IHD and first following pregnancy (mean years, [SD])	3.2 [3.2]	35
Parity at first following pregnancy after diagnosis of IHD		12
Nulliparous	30 (29%)	
Multiparous	74 (71%)	
Clinical presentation of IHD		12
Angina pectoris	8 (8%)	
Unstable angina pectoris	8 (8%)	
(N)STEMI	88 (85%)	
History of pregnancy related IHD	5 (4%)	
Underlying IHD pathology		45
Atherosclerosis	38 (54%)	
Thrombus/embolic	17 (24%)	
Coronary dissection	10 (14%)	
Coronary Spasm/normal coronaries	6 (8%)	
IHD treatment		28
None/Conservative/Medication only	35 (30%)	
Thrombolysis	2 (2%)	
PCI without stent	12 (14%)	
PCI with stent	17 (19%)	
PCI unknown	11 (13%)	
CABG	11 (13%)	
Comorbidities		
Obesity	14 (16%)	29
Dyslipidaemia	21 (20%)	11
Hypertension	35 (34%	11
Diabetes Mellitus	18 (18%)	13
Smoking	41 (40%)	14
Other heart disease	0	11
Heart failure	3 (3%)	11
CVA	2 (3%)	52
PE/DVT	2 (3%)	47
Hypercoagulation disorders	10 (16%)	54
Connective tissue disease	2 (3%)	53
Medication use		
*Anticoagulation **	23 (24%)	21
*Platelet inhibitors ***	45 (47%)	21
Betablocker	39 (42%)	23
Calciumantagonist	6 (7%)	23
Diuretic	5 (5%)	23
Statin	15 (16%)	23
Nitrate	17 (18%)	23
ATIIi/ACEi	21 (24%)	28
Medication use during pregnancy *		27
No anticoagulation or platelet inhibitors	32 (33%)	27
*Anticoagulation **	44 (45%)	27
VKA only	13 (13%)	
*VKA + single platelet inhibitors ***	12 (12%	
*VKA + dual platelet inhibitors ***	1 (1%)	
LMWH only	7 (7%)	
*LMWH + single platelet inhibitors ***	1 (1%)	
*LMWH + dual platelet inhibitors ***	2 (2%)	
VKA + 'heparin'	3 (3%)	
*VKA + 'heparin'+ single platelet inhibitors ***	4 (4%)	
UFH	1 (1%)	

To be continued on the next page.

Table 2. Continued.

Platelet inhibitors only	22 (22%	27
Single platelet inhibitor (ASA only)	14 (14%)	
*Dual platelet inhibitor ** *	6 (6%)	
*Triple platelet inhibitors ** *	0	
Dipyridamole only	1 (1%)	
Unknown platelet inhibitor	1 (1%)	
Betablocker	29 (31%)	32
Calciumantagonist	3 (3%)	37
Diuretic	8 (9%)	32
Statin	12 (14%)	36
Nitrate	19 (21%)	36
ATIIi/ACEi	10 (11%)	37
NYHA classification		50
1	52 (79%)	
2-4	14 (21%)	
LVEF		53
Normal (≥55%)	40 (64%)	
Mild dysfunction (45-54%)	13 (21%)	
Moderate dysfunction (35-44%)	9 (14%)	
Severe dysfunction (≤30%)	1 (2%)	

ACEi = angiotensin converting enzyme inhibitor, ASA = acetylsalicylic acid, ATIIi = angiotensin 2 inhibitor, CABG = coronary artery bypass grafting, CVA = cerebrovascular accident, DVT = deep venous thrombosis, IHD = ischemic heart disease, LVEF = left ventricular ejection fraction, (N)STEMI= (Non) ST-elevation myocardial infarction, NYHA = New York heart association, PCI = percutaneous coronary intervention, PE = pulmonary embolism, SD = standard deviation. *exact duration of use during pregnancy unknown; **including acetylsalicylic acid, clopidogrel, prasugrel, ticagrelor.

Table 3. Primary outcome endpoints and secondary cardiovascular complications in pregnancies in women with pre-existent IHD. Primary outcome endpoints are presented in bold font.

	All pregnancies (N,%)	**Missing data (N)**
Pregnancies	124	
Any cardiovascular complication	38 (32%)	7
Primary outcome complication	**29 (25%)**	**7**
Maternal death	**2 (2%)**	**10**
Cardiac arrest	**1 (1%)**	**10**
VT	**1 (1%)**	**13**
Angina Pectoris	**25 (22%)**	**1**
ACS	**10 (9%)**	**8**
Of which (N)STEMI	**8 (7%)**	
PCI	**3 (3%)**	**12**
CABG	**2 (2%)**	**11**
Heart Failure	2 (2%)	13
SVT	3 (3%)	12
New heart valve disease	1 (1%)	31
Endocarditis	0	12
CVA/TIA	2 (2%)	12
PE	1 (1%)	55
DVT	0	56

ACS = acute coronary syndrome, CABG = coronary artery bypass grafting, CVA = cerebrovascular accident, DVT = deep venous thrombosis, (N) STEMI= (non) ST elevation myocardial infraction, PCI = percutaneous coronary intervention, PE = pulmonary embolism, SVT = supraventricular tachycardia, VT = ventricular tachycardia, TIA = transient ischemic attack.

Table 4. Overview of the women with pre-existent ischemic heart disease (IHD) with pregnancies complicated by acute coronary syndrome (ACS).

Type of ACS	Age woman (years)	IHD Aetiology	Timing during / after pregnancy	Intervention	Obstetric complications	Foetal/neonatal complications
UAP	42	Atherosclerosis	15 weeks	CABG		miscarriage
UAP	41	Atherosclerosis	unknown	Unknown	Gestational DM Emergency CS	Hypoglycaemia
NSTEMI (maternal death)	41	Unknown	18 weeks	No		
NSTEMI	50	Unknown	8 weeks	PCI		Elective termination
NSTEMI	32	Thrombus/emboli	During pregnancy	Unknown	No	No
NSTEMI	33	Atherosclerosis	Post partum (4wk)	PCI	Pre-eclampsia	Prematurity (36 wks)
NSTEMI	32	Atherosclerosis	Post partum (4wk)	Unknown	Pre-eclampsia Emergency CS (maternal indication)	Prematurity LBI
NSTEMI	31	Coronary dissection	Post partum (5d)	No	No	No
NSTEMI	34	Coronary dissection	Post partum (9 wk)	CABG	No	No
STEMI	38	Unknown	6 wks	No	PIH	LBW, Foetal death (37 wks)

CABG= coronary artery bypass grafting, CS = Caesarean Section, DM = Diabetes Mellitus, LBW = low birth weight, NSTEMI = Non-ST-elevation myocardial infarction, PCI = percutaneous coronary intervention, STEMI = ST-elevation myocardial infarction, UAP = unstable angina pectoris.

Table 5. Obstetric complications.

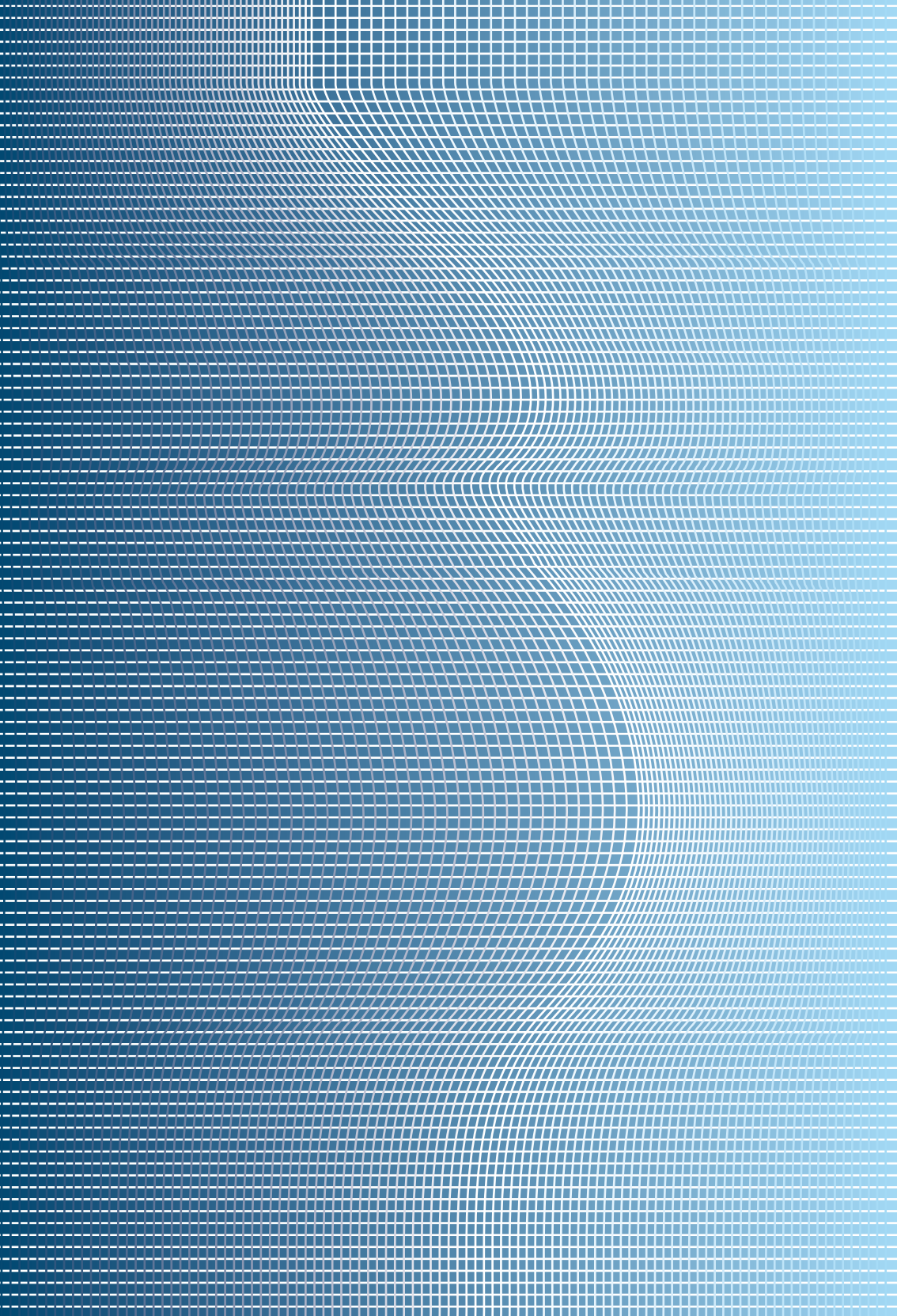
	All pregnancies (N,%)	Missing (N)
Completed pregnancies	112 *	
Mean timing of delivery (SD)	37 weeks (2.7 weeks)	14
Any obstetric complication	65 (58%)	
excl. planned CS **	38 (34%)	
Caesarean delivery	56(50%)	
Planned	36 (32%)	
Emergency maternal	10 (9%)	
Emergency foetal	7 (6%)	
Emergency unknown	7 (6%)	
Hypertensive disorders	23 (21%)	
PIH	11 (10%)	
Pre-eclamspia	12 (11%)	
Gestational diabetes mellitus	3 (3%)	20
PPH	6 (7%)	20

CS = Caesarean section, SD = standard deviation), PIH = pregnancy induced hypertension, PPH = post-partum haemorrhage. *Including 1 twin pregnancy. ** Any obstetric complication, planned CS (not for PIH/pre-eclampsia) excluded.

Table 6. Foetal/neonatal complications.

	All (N,%)	Missing (N)
Neonates	113*	
Feto-neonatal complications	47 (42%)	1
unrelated to planned CS	30 (27%)	1
Foetal/neonatal outcome		
Death >24wks	4 (4%)	
Death after life birth (40d)	1 (1%)	
Life birth	108 (96%)	
Prematurity	34 (32%)	5
IUGR	9 (10%)	25
LBW	26 (28%)	20
SGA	2 (4%)	62
Congenital disease	7 (6%)	4
Foetal haemorrhage	1 (1%)	29
ARDS	4 (5%)	29
Other serious complication **	5 (5%)	19

ARDS = acute respiratory distress syndrome, CS = Caesarean section, IUGR = intrauterine growth retardation, LBW = low birth weight, SGA = small for gestational age. *Including 1 twin pregnancy, ** hypoglycaemia (n=2), need for intubation due to meconium aspiration, (successful) neonatal cardiopulmonary resuscitation and nephrotic syndrome combined with neonatal sepsis (all n=1).



6

Pregnancy risks in women with pre-existing coronary artery disease, or following acute coronary syndrome

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Heart. 2015 Apr;101(7):525-9. doi: 10.1136/heartjnl-2014-306676

ABSTRACT

Objective

The objective of this study was to determine outcomes in pregnant women with pre-existing coronary artery disease (CAD) or following an acute coronary syndrome (ACS) including myocardial infarction (MI).

Background

The physiological changes of pregnancy can contribute to myocardial ischaemia. The pregnancy risk for women with pre-established CAD or a history of ACS/MI is not well studied.

Methods

This was a retrospective multicentre study. Adverse maternal cardiac, obstetric and foetal/neonatal events were examined. The primary outcome was a composite endpoint of cardiac arrest, ACS/MI, ventricular arrhythmia or congestive heart failure. The prevalence of new or progressive angina during pregnancy was also examined.

Results

Fifty pregnancies in 43 women (mean age 35±5 years) were included. Coronary atherosclerosis (40%) and coronary thrombus (36%) were the most common underlying diagnoses. The primary outcome occurred in 10% (5/50) of pregnancies and included one maternal death secondary to cardiac arrest. Other events included ACS/MI (3/50) and heart failure (1/50). New or progressive angina occurred in 18% of pregnancies. Ischaemic complications of any type (new or progressive angina, ACS/MI, ventricular arrhythmia, cardiac arrest) occurred more commonly in women with coronary atherosclerosis compared with those without (50% vs 10%, p=0.003). A high rate of adverse obstetric (16%) and foetal/neonatal (30%) events was observed.

Conclusions

Pregnant women with pre-existing CAD or ACS/MI before pregnancy are at increased risk of adverse events during pregnancy. Those with coronary atherosclerosis are at highest risk of adverse maternal cardiac events due to myocardial ischaemia during pregnancy.

INTRODUCTION

Current trends have led to an older age at the time of childbirth and increases in the prevalence of maternal diabetes, obesity and hypertension. These factors have contributed to a rising number of women of childbearing age with pre-existing coronary disease.[1–3] Ischaemic cardiac events, such as acute myocardial infarction (MI) have been associated with high maternal and foetal mortality.[4–6] While early case reports on pregnancy risk in women with pre-existing coronary artery disease (CAD) reported high maternal mortality,[7] subsequent case series reported improved maternal outcomes.[8 9] While many women with pre-existing CAD or a history of acute coronary syndrome (ACS) will consider pregnancy, the pregnancy risk for these women is not defined. The objective of this study was to determine maternal and foetal/neonatal outcomes in a large contemporary group of pregnant women with a history of CAD or ACS/MI prior to pregnancy.

METHODS

Study population

This was a multicentre review of pregnancies in women seen between 1995 and 2012 at one of the participating centres (University of Toronto, Toronto, Canada; University of British Columbia, Vancouver, Canada; Erasmus University, Rotterdam, The Netherlands; University Medical Centre, Groningen, The Netherlands; Academic Medical Centre, Amsterdam, The Netherlands; and University Medical Centre Utrecht, Utrecht, the Netherlands). This study was approved by the institutional review boards of the participating centres.

Cases were identified by systematic review of each institution's clinical database at each of the study centres. Inclusion criteria encompassed women referred with a history of CAD or an ACS, including MI, preceding pregnancy. ACS was defined as chest pain, electrocardiographic changes and abnormal biomarkers not meeting criteria for MI. MI was defined as elevated cardiac biomarkers (CK-MB, troponin) with at least one value above the 99th percentile and one of the following: symptoms of ischaemia, electrocardiographic changes, imaging evidence of new regional wall-motion abnormality or loss of viable myocardium, and/or identification of intracoronary thrombus by angiography.[10] Unstable angina and coronary spasm were clinical diagnoses made by the treating physician at the time of the previous clinical encounter. Women with first presentation of an ACS (including coronary dissection) during a pregnancy were not included. Women with Kawasaki disease or anomalous coronary arteries without history of ischaemic events were not included.

Baseline data

Demographic and clinical data were obtained from chart review and included maternal and gestational age, parity, earlier interventions, comorbidities (i.e., smoking history, diabetes, hypertension, inherited thrombophilia), New York Heart Association (NYHA) functional class, and medications. Assessment of LV systolic function was based on clinical reports and classified as: normal function (LVEF≥55%), mild (45%–54%), moderate (30%–44%) or severe (<30%) systolic dysfunction.[11]

Outcomes

The primary maternal cardiac outcomes of interest were cardiac arrest or cardiac death, sustained or symptomatic ventricular tachycardia, ACS, MI and pulmonary oedema. In one woman, a planned elective coronary artery bypass operation was delayed because of an unexpected pregnancy. The elective bypass took place postpartum, but was not considered an endpoint. Other outcomes of interest included new/progressive angina, thromboembolism and atrial arrhythmia requiring treatment. Cardiac adverse events were further classified as ischaemic (unstable angina, MI, ventricular tachyarrhythmia or cardiac arrest) or non-ischaemic.

Adverse foetal and/or neonatal events included premature birth (<37 weeks gestation), low birth weight (<2500 g), intrauterine growth retardation (foetal weight <10th percentile for gestational age), respiratory distress syndrome, intraventricular haemorrhage, spontaneous abortion (<24 weeks) and foetal or neonatal death.

Adverse obstetric events included pre-eclampsia (diagnosed by the treating physician) and postpartum haemorrhage (blood loss >500 mL after vaginal delivery or >1000 mL after caesarean section).[12]

Statistics

All data were analysed using SPSS V.16.0 (SPSS, Chicago, Illinois, USA). Normally distributed continuous variables were represented as a mean ±SD, and categorical variables were represented as a frequency. The differences between groups were determined using Student t test or χ^2 test; $p<0.05$ (two-sided) was considered to be significant.

RESULTS

During the study period, 50 pregnancies were identified in 43 women with pre-existing CAD or a history of ACS/MI prior to pregnancy. Baseline characteristics are summarised in table 1.

The majority of women (74%) were multiparous, and the mean study age was 34±5 years. Established risk factors for coronary disease were identified in 80% of women, the most common being a history of cigarette smoking, present in almost 60%.

The most common diagnoses were atherosclerosis (n=20) and intracoronary thrombus (n=18). Disorders of hypercoagulability were documented in seven women: Factor V Leiden mutation (n=3), antiphospholipid syndrome (n=3) and protein S deficiency (n=1). Less common findings included congenital fibroelastosis of the left main (n=1) and coronary spasm (n=5). Cardiac catheterisation had been performed prior to pregnancy in the majority of cases (n=39, 78%). Coronary atherosclerosis was diagnosed in 12 women at the time of cardiac catheterisation; these women were older (36±5 years), more likely to be multiparous (p=0.01) and to have multivessel disease (p<0.0001) versus women without atherosclerosis. Women diagnosed with intracoronary thrombus were younger and were more likely to be anticoagulated (p<0.0001). Eleven women did not undergo cardiac catheterisation after presenting with ACS. Coronary spasm was diagnosed by the treating physician as the aetiology of ACS in five women on the basis of their clinical presentation and investigation results. Aetiology was not documented in six women who met criteria for a history of ACS prior to pregnancy, but did not undergo cardiac catheterisation.

Previous cardiac interventions were documented in 54% (27/50) and included balloon angioplasty (n=5), coronary stent implantation (n=13), thrombolysis (n=6) and coronary artery bypass graft (CABG) surgery (n=3). Aspirin was the most common cardiac medication (n=27, 54%), followed by anticoagulants (n=12, 24%), β-blockers (n=38, 19%) and statins (n=4, 8%); the latter was stopped during pregnancy. ACE inhibitors had been used by 20% (10/50); these were discontinued prior to pregnancy in six women, and in the first trimester at the time of their first obstetric visit/cardiac review in the remaining four women.

Maternal cardiac outcomes

The primary outcome was observed in 10% (n=5) of pregnancies (tables 2 and 3, figure 1). There was one sudden death, 8 weeks postpartum, presumed secondary to ventricular arrhythmia in a woman with a history of MI and moderate LV systolic dysfunction. Two women with atherosclerotic coronary disease sustained MI during the postpartum period (at 4 and 8 weeks postpartum). Cardiac catheterisation revealed significant CAD leading to percutaneous coronary intervention in both patients. A 42-year-old woman with a history of coronary bypass graft surgery and normal LVEF presented with acute pulmonary oedema at 33 weeks gestation. Pulmonary oedema was attributed to a combination of factors including possible subclinical LV systolic dysfunction, demand ischaemia, and increased ventricular filling pressures. The patient responded

well to diuresis and short-term non-invasive positive pressure ventilation for the treatment of respiratory distress. Primary maternal cardiac events were more common in women with CAD due to coronary atherosclerosis (figure 1).

The primary adverse outcomes was not associated with maternal age (p=0.59), past/active smoking history (p=0.91), diabetes (p=0.30), revascularisation prior to pregnancy (p=0.71), atherosclerosis/CABG (p=0.64), multivessel disease (p=0.38), thrombophilia (p=0.34), reduced LVEF (p=0.39), aspirin use (p=0.78) or baseline anticoagulation (p=0.83).

Ischaemic cardiac events (new or progressive angina, ACS/MI, ventricular arrhythmia, cardiac arrest) complicated 26% of the pregnancies (tables 2 and 3). Treatment of angina, which complicated nine pregnancies, included clinical review alone (n=3), new antianginal therapy (n=2) and hospital admission with serial cardiac biomarkers for exclusion of MI (n=1). One woman had a normal stress echocardiogram at 38 weeks gestation. Two women underwent coronary angiography, one at 38 weeks gestation and the other 4 weeks postpartum. All were treated medically without angina recurrence, premature onset of labour, or foetal loss.

Women with pre-existing coronary atherosclerosis and/or CABG were at highest risk of ischaemic events (48% vs 10%, p=0.003). Other complications included supraventricular tachycardia in one woman and left frontal lobe embolic stroke in another; both women had a history of coronary thrombus (table 3). One woman with Ehlers–Danlos syndrome type IV (vascular type) developed bilateral dissection of the external iliac arteries 1 week postpartum.

Obstetric outcomes

Sixty-two percent of the deliveries were vaginal. Adverse obstetric outcomes occurred in 16% (n=8) of the pregnancies (table 4 and figure 1): pre-eclampsia in four women and postpartum haemorrhage in four women. Three of the four women diagnosed with pre-eclampsia had proven coronary atherosclerosis and two of four women in whom postpartum haemorrhage occurred were receiving anticoagulants for coronary thrombus. There were no deaths due to obstetric complications.

Foetal and neonatal outcomes

The median gestational age at live delivery was 38 weeks and median birth weight was 3050 g. Fifteen of 50 (30%) pregnancies were complicated by an adverse foetal/neonatal event (table 4 and figure 1). Three pregnancies ended in spontaneous abortion (<20 weeks gestation). One pregnancy ended in foetal death in utero due to twin–twin transfusion syndrome. There was also one foetal death 40 days postpartum in an infant born with trisomy 18. Preterm delivery (<37 weeks) occurred in 7 of 50 (14%) pregnancies. Low birth weight (<2500 g)

was documented in two pregnancies and intrauterine growth retardation in one. Adverse foetal/neonatal events occurred in 10 of the 20 women with coronary atherosclerosis (50%) and in four of the 18 with a history of coronary thrombosis/embolism (17%).

DISCUSSION

In developed nations, heart disease is the leading indirect cause of maternal death in pregnancy.[1 4] One specific cardiac condition seen with increasing prevalence in women of childbearing age is coronary disease. Despite an increasing number of young women with this condition, the risk of pregnancy in this group of women has not been well defined. In this study, we found that women with pre-established CAD or an ACS/MI prior to pregnancy were at risk for serious adverse maternal cardiac events (10% of pregnancies) during pregnancy. The highest rates of non-fatal ischaemic cardiac complications during pregnancy were experienced by women with atherosclerotic coronary disease.

Case reports and case series of pregnancy risk in women with MI prior to pregnancy report maternal mortality ranging between 0% and 23%.[7–9] The largest and most contemporary report describes 20 women included in the European Registry on Pregnancy and Heart Disease with an MI prior to pregnancy, in whom only one experienced new ACS in pregnancy and no mortality was observed.[9] We observed one maternal death in a woman with a history of MI and moderate LV dysfunction, who died suddenly at home 2 weeks postpartum. In this case, it is difficult to differentiate whether this event occurred secondary to the haemodynamic stress of pregnancy or was simply a manifestation of the natural history of LV dysfunction. Compared with earlier studies,[7 8] maternal mortality was significantly lower in this study. A number of factors may explain this. All were followed in tertiary cardiac care programmes in the contemporary era, the underlying aetiology of CAD/ACS/MI was identified and treated in most, many had undergone coronary revascularisation and almost all women had preserved ventricular function.

Existing tools for assessing global maternal cardiac risk in pregnancy are the CARPREG and ZAHARA risk scores.[12 13] These risk scores incorporate a range of clinical predictors including previous cardiac events (arrhythmia, heart failure), poor NYHA functional class, cyanosis, left heart obstruction and the presence of a mechanical valve. These risk scores, derived from cohorts of women with structural and congenital heart disease, were not developed to predict adverse outcomes in women with pre-established CAD or a history of ACS/MI. We found that a pre-existing diagnosis of coronary atherosclerosis was helpful in identifying those at highest risk of cardiac ischaemic events in pregnancy. It is

likely that other variables, such as ischaemia prior to pregnancy, multivessel disease or smoking, may better predict outcomes. Disease-specific complications remain important when stratifying risk, as illustrated by the patient in this study with Ehlers–Danlos syndrome whose pregnancy was complicated by vascular dissection. Sudden cardiac death in one woman with ischaemic cardiomyopathy is a reminder of the potential maternal morbidity and mortality associated with significant ventricular dysfunction.[9 14]

Obstetric, foetal and neonatal adverse events were common. Pre-eclampsia and low birth weight appeared to be more common in women with vascular disease (atherosclerosis and/or diabetes). This relationship may be a manifestation of the increased incidence of placental disease in women with systemic vascular disease and endothelial dysfunction.[15 16] We have previously compared the frequency of adverse neonatal outcomes in pregnant women with and without heart disease,[12] who were prospectively matched at the time of study enrolment. Neonatal adverse events were much more frequent in women with heart disease versus controls (18% vs 7%, respectively). In the present study, we observed a higher rate of adverse neonatal events (30%), which was primarily driven by early preterm labour and low birth weight/intrauterine growth restriction. Important differences exist in relation to this and our earlier study cohort, most notably a low prevalence of CAD (0.02%) and a predominance of women with congenital and valvular heart disease in the previous study. While the rate of neonatal complications in the current study is almost twice as high as that observed among women with congenital/valvular heart disease, it is premature to conclude that women with CAD or ACS/MI have worse neonatal outcomes. However, the increased rate of neonatal complications in this contemporary cohort of women with CAD or ACS/MI is concerning and deserves further research.

LIMITATIONS

The study has many limitations inherent to a retrospective observational study including small cohort size and the absence of a prospectively matched control group with which outcomes could be compared. Women included in this study were treated in maternity programmes linked to tertiary cardiac care centres, increasing the potential for referral bias. Women with less severe heart disease may not have been referred for specialist care. Women with more severe heart disease may have been advised against pregnancy. To attempt to minimise the impact of referral and/or institutional bias in care and patient outcomes, this study included women from two countries, Canada and the Netherlands. Despite this, outcomes may not reflect those achieved in less specialised centres and in lower-resource settings.[9]

In our study, age was not a major determinant of adverse events. This differs from other studies of MI in pregnancy which have reported that the risk of MI rises incrementally with maternal age,[17] so that by the age of 40 years, women have a 30-fold higher risk of cardiac ischaemia during pregnancy compared with women aged younger than 20 years.[5] It is possible that we failed to detect this association because of our relatively small cohort size.

In this study, the interval between previous MI and the onset of pregnancy was often not available, although this is an important determinant of outcome.[6] The risk of MI has also been reported to differ by race or ethnicity, black women reported to have the highest risk.[5] Racial differences in maternal cardiac risk were not a focus of this study, but may be important. An incidental observation was that women enrolled from The Netherlands had a high rate of factor V Leiden deficiency associated with intracoronary thrombus. To identify predictors of outcomes in this patient population, prospective studies in larger sample sizes are needed.

CONCLUSION

Women with a pre-existing CAD or following ACS/MI are at increased risk of adverse maternal cardiac events in pregnancy. They are also at increased risk of obstetric, foetal and neonatal complications. The presence of coronary atherosclerosis identifies women at highest risk of cardiac ischaemic events during subsequent pregnancy. This information will be helpful for the clinician; aiding in preconception counselling and risk stratification.

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TABLES AND FIGURES

Table 1. Baseline characteristics.

Demographic factors	N (%)
Women	43
Pregnancies	50
Mean age at delivery (years)	35 ± 5
Age range (years)	27 - 47
Multiparous	37 (74)
Cardiac diagnosis	
Atherosclerosis	20
Coronary thrombus or embolism	18
Coronary spasm	5
Acute coronary syndrome[a]	6
Pre-existing coronary risk factors	
≥ 1 risk factor	41 (82)
Smoking	11 (22)
Family history	22 (44)
Hypertension	18 (36)
Dyslipidaemia	10 (20)
Obesity	5 (10)
Diabetes	4 (8)
Thrombophilia[b]	7 (14)
Cardiac medications at first antenatal visit* n=44	
Any medication	47 (94)
Aspirin / Clopidogrel	28
Beta-blocker	19
Heparin	8
Warfarin	6
ACE inhibitor	8
NYHA functional class at first antenatal visit	
I	42
II - IV	8
Left ventricular systolic function[c] n=45	
Normal	27 (54)
Mildly reduced	13 (26)
Moderately reduced	5 (10)

CABG = Coronary artery bypass graft surgery; ECG = Electrocardiogram; LV = Left ventricle; NYHA = New York Heart Association. Note: Coronary anatomy findings are mutually exclusive. *Medications not documented in 6 pregnancies. a. Acute coronary syndrome documented but aetiology not specified. b. Thrombophilia [Factor V Leiden (n=3), Antiphospholipid syndrome (n=3), Protein S deficiency (n=1)] confirmed with genetic/lab testing. c. Left ventricular function assessed by transthoracic echocardiogram at first antenatal visit.

Table 2. Adverse maternal cardiac events during pregnancy.

	Primary cardiovascular endpoint				Secondary cardiovascular endpoint			
	Any primary event	Cardiac arrest / ventricular arrhythmia	ACS/MI	Heart failure	Any secondary event	Angina	Stroke / PE	Atrial arrhythmia[a]
Total	5 (10)	1	3	1	12 (24)	9	2	1

ACS = Acute coronary syndrome, MI = Myocardial infarction, PE = Pulmonary embolus. Angina defined as clinical diagnosis by the treating physician resulting in admission or up-titration of anti-anginal medications. a. Supraventricular tachycardia at 39 weeks gestation.

Table 3. Timing of adverse maternal cardiac events.

Maternal cardiac diagnosis	Maternal Age (years)	Cardiac event	Gestation (weeks)
Primary cardiac events			
Presumed coronary artery spasm and MI	27	Sudden death	8 weeks post-partum
Coronary atherosclerosis	42	CHF	33 weeks
Coronary thrombus	32	ACS	34 weeks
Coronary atherosclerosis	33	MI	4 weeks post-partum
Coronary atherosclerosis	32	MI	8 weeks post-partum
Other cardiac events			
Coronary thrombus	40	CVA	5 weeks
Coronary atherosclerosis	34	Angina	12 weeks
Coronary atherosclerosis	41	Angina	20 weeks
Coronary thrombus	33	Angina	21 weeks
Coronary fibroelastosis	27	Angina	24 weeks
Coronary atherosclerosis	28	Angina	30 weeks
Coronary atherosclerosis	30	Angina	32 weeks
Coronary atherosclerosis	36	Angina	33 weeks
Coronary atherosclerosis	41	Angina	36 weeks
Coronary thrombus	28	SVT	39 weeks
Ehlers-Danlos Syndrome	32	Iliac artery dissection	1 week post-partum
Coronary atherosclerosis	34	Angina	4 weeks post-partum

ACS = Acute coronary syndrome, CABG = Coronary artery bypass grafts, CHF = Congestive heart failure, CVA = Cerebrovascular accident, MI = Myocardial infarct, SVT = Supraventricular tachycardia.

Table 4. Adverse obstetric, foetal and neonatal outcomes.

	Pregnancies N (%)
Adverse obstetric outcomes	
Total events	8 (16)
Pre-eclampsia	4 (8)
Post-partum haemorrhage	4 (8)
Non-cardiac death	0 (0)
Adverse foetal/neonatal outcomes*	
Total events	15 (30)
Pre-term delivery (<37 weeks)	7 (14)
Low birth weight	2 (4)
Intrauterine growth retardation	1 (2)
Intraventricular haemorrhage	0 (0)
Respiratory distress	0 (0)
Spontaneous abortion[a]	3 (6)
Foetal death[b]	1 (2)
Neonatal death[c]	1 (2)

Spontaneous abortion refers to miscarriage prior to 20 weeks gestation. b. One pregnancy ended with foetal death due to twin to twin transfusion syndrome. c. Neonatal death occurred 40 days post-partum in an infant born with Trisomy 18.

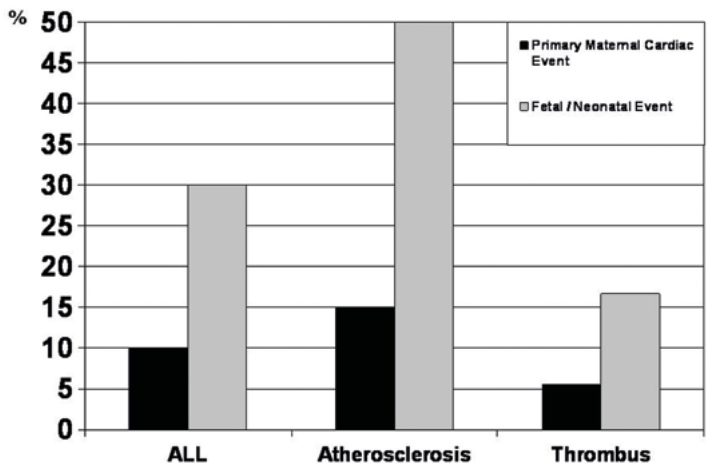

Figure 1. Frequency of maternal cardiac and foetal/neonatal events during pregnancy in women pre-existing coronary artery disease or following an acute coronary syndrome.

7

Biological versus mechanical heart valve prosthesis during pregnancy in women with congenital heart disease.

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Int J Cardiol. 2018 May 23. doi: 10.1016/j.ijcard.2018.05.038.

ABSTRACT

Background

We evaluate pregnancy outcome and anticoagulation regimes in women with mechanical and biological prosthetic heart valves (PHV) for congenital heart disease.

Methods

Retrospective multicentre cohort studying pregnancy outcomes in an existing cohort of patients with PHV.

Results

52 women had 102 pregnancies of which 78 pregnancies (46 women) ≥20 weeks duration (59 biological, 19 mechanical PHV). Miscarriages (n=19, ≤ 20 weeks) occurred more frequently in women using anticoagulation (p<.05). During 42% of pregnancies of women with mechanical PHV a combined low molecular weight heparin (LMWH) vitamin-K-antagonist anticoagulation regime was used (n=8). Overall, cardiovascular, obstetric and foetal/neonatal complications occurred in 17% (n=13), 68% (n=42) and 42% (n=27) of the pregnancies. Women with mechanical PHV had significantly higher cardiovascular (12% vs 32%, p<.05), obstetric (59% vs 85%, p=.02) and foetal/neonatal (34% vs 61%, p<.05) complication rates than women with biological PHV. This was related to PHV thrombosis (n=3, p<.02), post-partum haemorrhage (p<.02), caesarean section (p<.02), low birth weight and small for gestational age (both p<.05). PHV thrombosis occurred in 3 pregnancies, including 2/5 pregnancies with pulmonary mechanical PHV. PHV thrombosis was related to necessary cessation of anticoagulation therapy or insufficient monitoring of LMWH. Other cardiovascular complications occurred equally frequent in both groups.

Conclusion

Complications occur more often in pregnancies of women with a mechanical PHV than in women with a biological PHV, mainly caused by PHV thrombosis and bleeding complications. Meticulous monitoring of anticoagulation in pregnant women is necessary. Women with a pulmonary mechanical PHV are at high risk of complications.

INTRODUCTION

A growing number of adult women with congenital heart disease (CHD) is treated with prosthetic heart valves (PHV). Still, the choice of type of valve prosthesis is difficult in young women with future desire to become pregnant.

While current European guidelines advise to consider implantation of a biological PHV in women with a pregnancy wish, the underlying evidence is limited.[1] The high deterioration rate of biological PHV at young age poses the woman at risk of going through pregnancy with a stenotic or regurgitant PHV.[2] Young women with a biological PHV inevitably face re-operation because of valve deterioration, with associated risks. Whether or not pregnancy itself accelerates the deterioration rate of PHVs is a debated controversy.[2-5]

Mechanical PHV necessitate anticoagulation therapy, but there are no anticoagulation regimens that are sufficiently proven to be effective as well as safe for both mother and child.[6-9] Vitamin K antagonists (VKA) are associated with increased risk of pregnancy loss and with embryopathy, especially at higher dosages.[10] Anticoagulation with unfractionated or low-molecular weight heparin (UFH or LMWH) appears to be associated with increased risk of PHV thrombosis, even with monitoring of anticoagulation effect and dose adjusting.[9 11-13] Current anticoagulation advices are largely based on expert opinion since randomized studies are lacking and reported series are often small.[6 14] European and American guidelines advise the use of a combined regimen of VKA and LMWH in a substantial proportion of pregnancies, but there are relatively few data to support this advice.[9 15] Furthermore, data concerning outcome of pregnancies in women with right sided mechanical PHVs are scarce.[9 11 12 16] Even less is known about non-cardiac (obstetric and foetal/neonatal) complications and their relation with cardiac complications and PHV type in pregnant women with PHV. With insufficient evidence, an explicit preference for either biological or mechanical PHV in young women who wish to become pregnant is hard to substantiate. We therefore aim to perform a retrospective multicentre cohort study to evaluate and compare cardiovascular, obstetric and foetal/neonatal outcomes of pregnancy in women with mechanical and biological PHV for CHD and discuss anticoagulation regimen.

METHODS

Patient inclusion

We recruited women with pregnancy after PHV implantation from the Dutch PROSTAVA (PROSTheses in Adult congenital heart VAlve disease) study. This study primarily aims to investigate functional outcome related to PHV characteristics in patients with CHD.[17] The secondary aim is to retrospectively

evaluate PHV complications, including pregnancy-related complications, which was the primary goal of our sub study.[18-20] The study has been approved by the institutional review board of all participating centres. For the PROSTAVA study, patients with CHD and a PHV were identified through the Dutch national CONCOR database, founded in 2001.[21] CONCOR registers all adults with CHD in the Netherlands with their informed consent.[21] All women enlisted in the PROSTAVA database who had been pregnant after PHV implantation were included in the current analysis. Data were collected from their medical files. A detailed and structured questionnaire was obtained from women who had given their consent to be contacted by PROSTAVA investigators, in order to clarify and supplement data from the medical files. Complications identified through the questionnaire were only registered when confirmed by medical files.

End points

Our primary endpoint consisted of cardiovascular complications during pregnancy and up to 6 months after pregnancy. Secondary endpoints were obstetric, foetal/neonatal and general pregnancy outcomes. Furthermore, we evaluated anticoagulation regimes in women with a mechanical PHV and the possible relation with complications.

Collected data

Only pregnancies after implantation of PHV were taken into account. Baseline characteristics included age, underlying heart disease, PHV characteristics (type, size, location, date of implantation and times of re-surgery), history of prosthesis-related complications as defined by previously published guidelines (including valve deterioration, valve thrombosis, embolism, haemorrhage and endocarditis), history of other cardiovascular complications (including documented and treated heart failure and any documented pre-pregnancy arrhythmias needing treatment) and general medical history.[22] Pregnancies were defined as completed (>20 weeks and not abortus provocatus) or incompleted (≤20 weeks or abortus provocatus).

Pregnancy related complications were collected for all pregnancies and analysed for completed pregnancies and defined as occurring during pregnancy and up to 6 months postpartum. Pregnancy related complications were defined in accordance with our previous studies and according to guidelines.[20 22 23] We collected prosthesis related cardiovascular complications (including valve deterioration, valve thrombosis, embolism, haemorrhage, endocarditis and haemolytic anaemia), other cardiovascular complications (including need for urgent invasive non-prosthesis related cardiovascular procedures, heart failure or arrhythmias requiring (change of) treatment, myocardial infarction, intensive care or coronary care unit (IC/CCU) admission). Furthermore we collected New York Heart Association (NYHA) class deterioration ≥2 points as a secondary cardiovascular outcome measure.[22]

For evaluation of anticoagulation regimes data concerning anticoagulation medication and monitoring before and during pregnancy were retrieved from medical files. Obstetric complications were defined in line with previous papers of our group as primary obstetric events (including assisted delivery (forceps/vacuum extraction, elective or emergency Caesarean Section), pregnancy induced hypertension, (pre)eclampsia, HELLP syndrome, non-cardiac death, postpartum haemorrhage (blood loss >500 mL (vaginal delivery) or >1000 mL (caesarean section), >1mmol/L drop in haemoglobin levels or need for transfusion therapy), haemorrhage from the placenta, premature labour, preterm prelabor rupture of membranes) and induction of labour as a secondary obstetric event. General maternal complications included haemorrhage (not postpartum, defined as an estimated loss of >0.5 L of blood, >1mmol/L drop in haemoglobin levels or need for transfusion therapy or documented intracerebral bleeding), hospitalization >1 night, anaemia, maternal infection and fever.[23]

Foetal/neonatal complications were defined as previously described and included foetal/neonatal death (death after ≥20 wks. of gestation up to 28 days postpartum), neonatal respiratory distress syndrome, infection leading to hospital admission, neonatal intensive care unit (NICU) admission, premature birth (birth <37 wks. gestation, spontaneous or iatrogenic), low birth weight (birth weight <2500 grams), small for gestational age (birth weight <10th percentile, adjusted for gestational age, based on population values), occurrence of CHD or other congenital disease in the offspring and Apgar-score<7 (at one and five minutes after birth). [23]

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics Premium' V 22 for Windows (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, version 22.0. Armonk, NY: IBM Corp.) Missing data were excluded for analysis. Continuous data are presented as mean with standard deviation (SD) or median with interquartile range (IQR) or range, depending on their distribution. Normality was tested with the Kolmogorov-Smirnov test with Lilliefors' correction. Absolute numbers and percentages were presented for categorical data. We used the Chi-square test for comparison of categorical variables, the independent t-test for comparison of two means, Pearson correlation for correlation coefficients and the Kruskall Wallis test for comparison of non-parametric data. A $p \leq .05$ was considered statistically significant, all tests are two-tailed.

RESULTS

Fifty-one women had 102 pregnancies after PHV implantation, of which 28 pregnancies (28%) occurred in women with a mechanical PHV. Pregnancies occurred from 1991 to 2013.

INCOMPLETED PREGNANCIES

Data concerning all pregnancies including incompleted pregnancies (n=24) are displayed in table 1. Six women had a miscarriage within the first trimester, timing of the miscarriages of the other women were unknown (by definition ≤20 wks).

Warfarin embryopathy was not reported. One woman with a biological PHV used anticoagulation therapy (VKA, unknown indication), as did all women with mechanical PHV (VKA or LMWH). Use of anticoagulation therapy (VKA or LMWH) was associated with miscarriages (47% vs. 24%, r=.2, p<0.05). Six out of eight women (75%) with mechanical PHV used VKA during their non-vital pregnancies or spontaneous abortions, two women used LMWH (n.s.).

COMPLETED PREGNANCIES

Baseline characteristics

Baseline characteristics for 46 women with completed pregnancies (n=78) are described in *table 1.*

Primary outcome

Overall, cardiovascular complications during pregnancy were observed in 17% (n=13), obstetrical complications in 68% (n=42) and foetal/neonatal l complications in 42% (n=27) of the pregnancies in women with a PHV for CHD, see figure 1. The chances of going through a completed pregnancy without cardiovascular, primary obstetric or foetal/neonatal events was 30% (n=13, missing data in n=16) in women with biological PHV and 6% (n=1, missing data in n=1) in women with mechanical PHV, p<0.05.

Cardiovascular complications

Data concerning cardiovascular complications are presented in table 2.

Thrombo-embolic complications

PHV thrombosis occurred during 3 pregnancies in 3 women with a mechanical PHV (16%) (table 2 and 3). Two out of 3 women with a pulmonary mechanical PHV had a PHV thrombosis during a total of 5 pregnancies (40%). One woman with a pulmonary PHV (St. Jude Medical) had a PHV thrombosis the 1st day post-partum after cessation of intravenous unfractioned heparin (UFH) anticoagulation therapy because of severe post-partum haemorrhage. Another woman with a pulmonary PHV (St. Jude Medical) had a PHV thrombosis in the 2nd trimester while on LWMH therapy without anti-Xa monitoring. She was treated with thrombolysis and continued her pregnancy using VKA. The third woman had an aortic PHV (St. Jude Regent) thrombosis 3 times during 1 pregnancy. She

presented at 20 weeks of pregnancy with PHV thrombosis while she used VKA. In hindsight, her thrombosis had, based on her medical history of a cold arm and immeasurable blood pressure in that arm, probably developed 8 weeks earlier when she used LMWH therapy without anti-Xa level monitoring. She was successfully treated with thrombolysis but developed 2 recurrent episodes of valve thrombosis in the second and third trimester despite intensified LMWH therapy with anti-Xa level monitoring (anti-Xa levels ranging from 0,24 – 0, 92 U/l) for which she repeatedly received thrombolysis.

Other cardiovascular complications

Heart failure occurred in 2 women with biological PHV. In one woman with structural PHV failure occurred 9 years after implantation (aortic PHV), and in another woman after CS in a triplet pregnancy complicated by pre-eclampsia (pulmonary PHV). Heart failure in 2 women with mechanical PHV occurred around delivery in a woman with a mechanical AVR, PVR and MVR who had a compromised LV function, and in a woman with a mechanical AVR and MVR, this woman had a SVT earlier in the same pregnancy for which she used metoprolol.

Secondary outcomes

Anticoagulation regimes and related complications

Details concerning anticoagulation regimes and complications during pregnancies in women with mechanical PHV (n=19) are presented in table 3. A regime in which women switched from VKA to LMWH in the first trimester of pregnancy, with restart of VKA in second trimester, was used most frequently (n=7). In 3 pregnancies in which women were anticoagulated with LMWH (n= 11, partly or throughout), anti-Xa monitoring was reported (27%). All women used (low molecular) heparin around the delivery.

Post-partum haemorrhage (PPH) occurred in 50% of the pregnancies in women with mechanical heart valves, significantly more compared to pregnancies in women with biological PHV, as presented in table 2.

Other significant haemorrhagic events (vaginal, hematoma of the extremities and paracolpium) occurred in 2 pregnancies in the same woman, during heparin therapy combined with thrombocyte aggregation inhibitors.

Obstetric complications

Data concerning primary obstetric complications in pregnancies in women with PHV could be sufficiently retrieved in 62 pregnancies (80%) and are presented in table 2. Obstetric complications occurred significantly more often in women with mechanical PHV than in women with biological PHV. Primary obstetric complications co-occurred in all but one (n=12, 92%)) of the pregnancies with cardiovascular complications, significantly more than the occurrence of

obstetric complications in pregnancies without cardiovascular complications (n=30, 61%), p=.03. Obstetric complications in pregnancies with cardiovascular complications were CS (n=8), pre-eclampsia (n=3), PIH (n=1) and PPH (n=4). In women with biological PHV none of the emergency CS (n=3) were performed for cardiovascular indication, planned CS (n=4) was performed for maternal cardiovascular indication once (valve failure). Emergency (n=4) and planned (n=5) CS in women with mechanical PHV were performed for maternal cardiovascular indication 3 times (PHV thrombosis in 2 women and aortic dissection in 1).

General complications

General complications are listed in tables 2.Anemia occurred in in the first week post-partum (n=14) and was related to PPH in 93% (n=13). Most hospital admissions were for labour and delivery.

Foetal/neonatal complications

Foetal/neonatal outcome is presented in tables 2 an 3.Fetal/neonatal complications occurred significantly more often in women with mechanical PHV mainly due to a higher incidence of SGA and LBW. Three out of five neonates who were delivered by planned CS in women with mechanical PHV, were delivered prematurely (1 for maternal cardiovascular complication, 2 unknown reason). All foetal/neonatal complications occurred in pregnancies with primary and/or secondary obstetric complications (r=.46, p<.001). Congenital disease in the offspring occurred 3 times, one had Marfan syndrome, and two CHD (hypoplastic left heart syndrome, this baby died; and ventricular septal defect).

DISCUSSION

In this series of 102 pregnancies in women with prosthetic heart valves we found that women with PHV have a high incidence of cardiovascular, obstetric and foetal/neonatal complications during pregnancy. The miscarriage rate was high in women who used anticoagulation therapy. Women had an overall low chance of going through an uneventful pregnancy. Women with a mechanical PHV had a significantly lower chance of an uneventful pregnancy compared to women with a biological valve. This was due to the higher rate of cardiovascular, obstetric and foetal/neonatal complication rates in women with mechanical PHV. This was mainly caused by PHV thrombosis and bleeding complications in the women with mechanical PHV. Pulmonary mechanical valves accounted for 2 out of 3 PHV thromboses. All three cases of PHV thrombosis were related to necessary cessation of anticoagulation around delivery or to (in hindsight, according to current guidelines but not necessarily according to state of the art at the time of the event) insufficient (monitoring of) anticoagulation. Bleeding complications (mostly PPH) were more frequently seen in pregnancies in women with mechanical PHV.

Incompleted pregnancies

Non-vital pregnancies and spontaneous abortion rates in women with biological PHV are comparable to miscarriage rates reported in other women with CHD. However, in women with a mechanical valve the miscarriage rate was high (30%) and associated to the use of anticoagulation therapy. Miscarriages appeared to occur especially during the use of VKA therapy, in line with previous literature.[3 9 24 25] Recent literature suggests that the miscarriage rate is significantly lower in women needing low dosages of VKA or in women who switch to LMWH or UFH during the 6-12th week of pregnancy.[10 15 26 27]

Completed pregnancies

Anticoagulation regimes

Current guidelines advise an individualized approach to anticoagulation in pregnant women with mechanical PHV. Women who use low dose VKA therapy (2 pregnancies in this study) are advised to continue this treatment until a few weeks before delivery, because of the effective protection from PHV thrombosis and the relatively low risk of embryopathy and pregnancy loss. In our study, 7 women with a mechanical PHV used predominantly LMWH in the first trimester with a switch to VKA in the second trimester. Interestingly, although this regimen is recommended in current American and European guidelines[1 6 14] the number of pregnancies described with this regimen is limited (N=60).[9 13 15] None of the women who used LMWH throughout had thrombotic or bleeding complications during pregnancy, however, this concerned only 3 pregnancies. A recent prospective population-based study from the UK reported a high incidence of maternal and foetal/neonatal complications, including 9% maternal mortality and PHV thrombosis in another 16% of the pregnancies in women who were largely anticoagulated with LMWH throughout pregnancy. [13]

PHV thrombosis

The occurrence of PHV thrombosis was responsible for the significant difference in cardiovascular complications between pregnancies in women with mechanical and biological PHV. This may be related to LMWH therapy; when LMWH is used during pregnancy, the dose needs to be increased due to an increased glomerular filtration rate and renal clearance of LMWH. Therefore, current guidelines recommend that LMWH is only used in women with mechanical PHV when close monitoring of anti-Xa levels is performed.[6 7 11 12 14 28] The optimal range of anti-Xa levels, whether to measure peak or through levels and interval of measurements is still debated.[6 11-13] Current European guidelines recommend maintaining peak anti-Xa-levels between 0.8 and 1.2 U/ml, but higher target levels (possibly 1.0-1.2 U/ml) may be necessary.[13 6] In 8 out of 11 pregnancies anti-Xa level monitoring was not performed while using LMWH therapy, of which 4 pregnancies occurred before guidelines recommendations.[29 30] In 2 pregnancies in which anti-Xa monitoring was not performed PHV thrombosis occurred. In 1 woman the

thrombosis recurred twice during LMWH with anti-Xa level monitoring with, in hindsight according to recent literature, too low targeted anti-Xa levels.[13] No evidence-based advice regarding the frequency of anti-Xa monitoring exists, but experts recommend weekly anti-Xa controls. [6 13] Additionally, the data from a recent study suggest that a higher starting LMWH dose than the usual weight-base recommended dose may be advisable in these pregnant women.[13]

It is striking that two out of the three PHV thromboses occurred in bi-leaflet pulmonary PHV's, though only 5 of the 19 pregnancies with mechanical PHV involved a pulmonary mechanical PHV. It is also notable that in one woman who had 3 mechanical valves, only the pulmonary valve thrombosed. While one of the pulmonary PHV thromboses could possibly have been prevented by adequate anti-Xa monitoring, the other occurred during necessary interruption of heparin therapy because of severe PPH. These two pulmonary PHV's were also mentioned in our previous study on the outcome of patients with mechanical pulmonary PHV.[18] Our current study adds a different perspective to these cases, and reveals that pulmonary mechanical PHV's are probably more vulnerable for thrombosis during pregnancy than valves in other positions. While mechanical pulmonary valve implantation is only performed in few centres in the world, it is probably best avoided in women of fertile age who may have a future desire to get pregnant.[18]

Bleeding complications

Bleeding complications occurred significantly more often in pregnancies in women with mechanical PHV. The incidence of PPH in women with mechanical PHV was 5-20 times higher than its incidence in women with CHD in general or in women with high maternal cardiovascular risk (WHO class III).[31-33] Contemporary American guidelines recommend to add a thrombocyte aggregation inhibitor to the VKA in the second and third trimester.[14] In our study these were the only pregnancies (n=2) in which haemorrhage (not PPH) occurred. Similar findings were recently reported in the ROPAC study.[9] Since the benefit of thrombocyte aggregation inhibitors in addition to VKA is not proven while 2 studies report increased bleeding complications, the addition of thrombocyte aggregation inhibitors to VKA seems not advisable.

Other cardiac complications

Other cardiac complications (heart failure and arrhythmia) occurred frequently but were not related to PHV type and their incidence is comparable to pregnancies in women with other CHD.[31 33-35] In both cases of biological PHV failure the risk of failure was already high pre-pregnancy.[2 36 37] Women with a mechanical valve often had a history of re-surgery related to deterioration of a biological valve before pregnancy. Our data therefore illustrate that despite the better pregnancy outcome implantation of a biological PHV is not automatically the best choice in women with a desire to get pregnant.

Obstetric and foetal/neonatal complications

Obstetric complications occurred in almost all pregnancies with cardiovascular complications and significantly more frequently in pregnancies in women with mechanical PHV. We included assisted deliveries in our primary obstetric complications as we used to do in our previous publications[23], because the choice for assisted delivery will often be driven by the heart disease and in women without heart disease other choices would have been made. The overall incidence of obstetric complications may have been increased by this inclusion, however, these was no significant difference in incidence of assisted delivery for pregnancies in women with mechanical PHV versus biological PHV. The higher incidence of obstetric complications in pregnancies in women with mechanical PHV was mainly due to the significant higher rate of CS and PPH in these pregnancies. Planned CS was observed frequently as mode of delivery in women with mechanical PHV. While vaginal delivery is usually preferred and CS is generally reserved for obstetric indications, planned CS can be considered according to guidelines in women with mechanical PHV to minimize the time on LMWH or heparins and the time without anticoagulation (and therefore minimize maternal thrombotic risk).[6] Furthermore, vaginal delivery while the mother uses VKA is contra-indicated, because of the risk of foetal intracranial haemorrhage.[6] Switching anticoagulation therapy from VKA to LMWH or heparins in the 36th week of pregnancy is therefore advised[1 6] All foetal/neonatal complications in completed pregnancies occurred in pregnancies with obstetric complications. Especially LBW and SGA occurred more often in pregnancies of women with a mechanical PHV. We could not relate this to anticoagulant therapy, nor to cardiovascular or obstetric complications. However, while not statistically significant, the incidence of prematurity was >2 times higher in neonates from women with mechanical PHV. This may be related to the higher rate of planned CS in women with mechanical PHV, causing prematurity in 3 out of 5 neonates.

LIMITATIONS

The women included in our study were mostly treated in a tertiary hospital which may have biased the results. However, most women with a mechanical valve are treated in tertiary care centres, especially during pregnancy. Furthermore, we could not reliably present mortality rates because data were primarily retrieved from a survival cohort. Limited data concerning anti-Xa measurements deprived us of substantiated statements of LMWH therapy during pregnancy.

CONCLUSION

Women with PHV have a high incidence of cardiovascular, obstetric and foetal/neonatal complications during pregnancy or the post-partum period. The higher incidence in complications in pregnancies in women with mechanical PHV was mainly related to the higher occurrence of PHV thrombosis, and pulmonary mechanical PHV appeared at especially high risk. PHV thrombosis occurred during periods of inadequate monitoring of anticoagulation or necessary interruption of anticoagulation. Because biological valve deterioration with the necessity for valve replacement appears to occur often in young women even before they get pregnant, the choice for a biological PHV in these young women is not indisputable.

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TABLES AND FIGURES

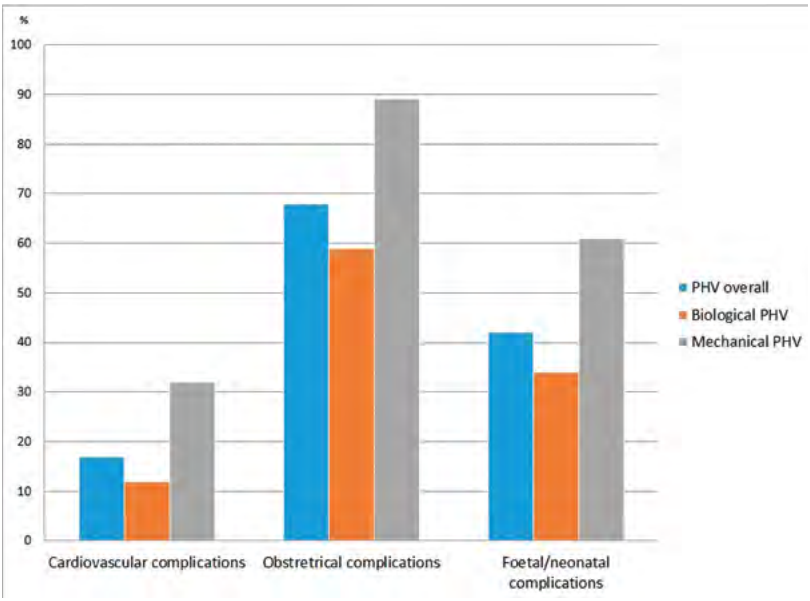


Figure 1. The occurrence of cardiovascular, primary obstetrical and foetal/neonatal complications during pregnancy or the post-partum period in women with biological of mechanical PHV.

Table 1. Baseline characteristics for pregnancies in women with PHV for CHD.

		Valve Type		
	All	**Biological PHV only**	**Mechanical PHV/ Combined**	
Women, all (N)	52	40	12	
Pregnancies, all (N)	102	74	28	
Abortus provocatus (N)	5	4	1	
Miscarriages (N, %)	19 (19%)	11 (16%)	8 (30%)	p=.12
Women with completed pregnancies (N)	46	36	10	
Completed pregnancies (N)	78	59	19	
Underlying heart disease * (N women)	Congenital AOV	20	8	
	ToF	6	1	
	PS	8	0	
	Marfan	0	1	
	Other	2	0	
Location of PHV * (N pregnancies)	AVR	19	9	
	PVR	26	2	
	MVR	2	0	
	PVR + AVR	12	3	
	MVR + AVR	0	3	
	PVR + AVR + MVR	0	2	
Pre-pregnancy re-surgery for PHV * (N pregnancies) (%)	16 (21%)	8 (14%)	8 (42%) ‡	*p<.02*
Pre-pregnancy cardiovascular and prosthesis related history * (N pregnancies)	Rhythm disorder	8	5	
	Heart failure	3	4	
	Arterial thrombosis	1	0	
	PVLeakage	0	3	
	Infection	0	3	
	Trombo-embolism	0	1	
Gravida *	1 (1-8)	1 (1-6)	2 (1-8)	
Parity *	0 (0-4)	0 (0-4)	1 (0-3)	
Nulliparous * (%)	(39) 55%	30 (58%)	9 (47%)	
Age at pregnancy * (years, range)	29 (20-41)	29 (20-41)	30 (23-40)	
Time between last PHV surgery and pregnancy *(years, range)	6 (0-22)	6 (0-21)	6 (2-22)	

Completed pregnancies: >20 weeks and not abortus provocatus. Incompleted pregnancies: ≤20 weeks or abortus provocatus. Missing data were excluded for analysis. *Analysis performed in completed pregnancies, AVR = aortic valve replacement, CHD = congenital heart disease, Congenital AOV= congenital aortic valve disease including aortic stenosis, aortic regurgitation and bicuspid aortic valves, Cong PS = congenital pulmonic valve stenosis, MVR = mitral valve replacement, PHV = prosthetic heart valve(s), PVLeakage = paravalvular leakage, PVR = pulmonary valve replacement, ToF = Fallots tetralogy. ‡ Re-surgery was related to deterioration of a biological PHV even before pregnancy could occur in 2 women.

Table 2. Cardiovascular, primary obstetric and foetal/neonatal outcome and complications in completed pregnancies in women with PHV for CHD.

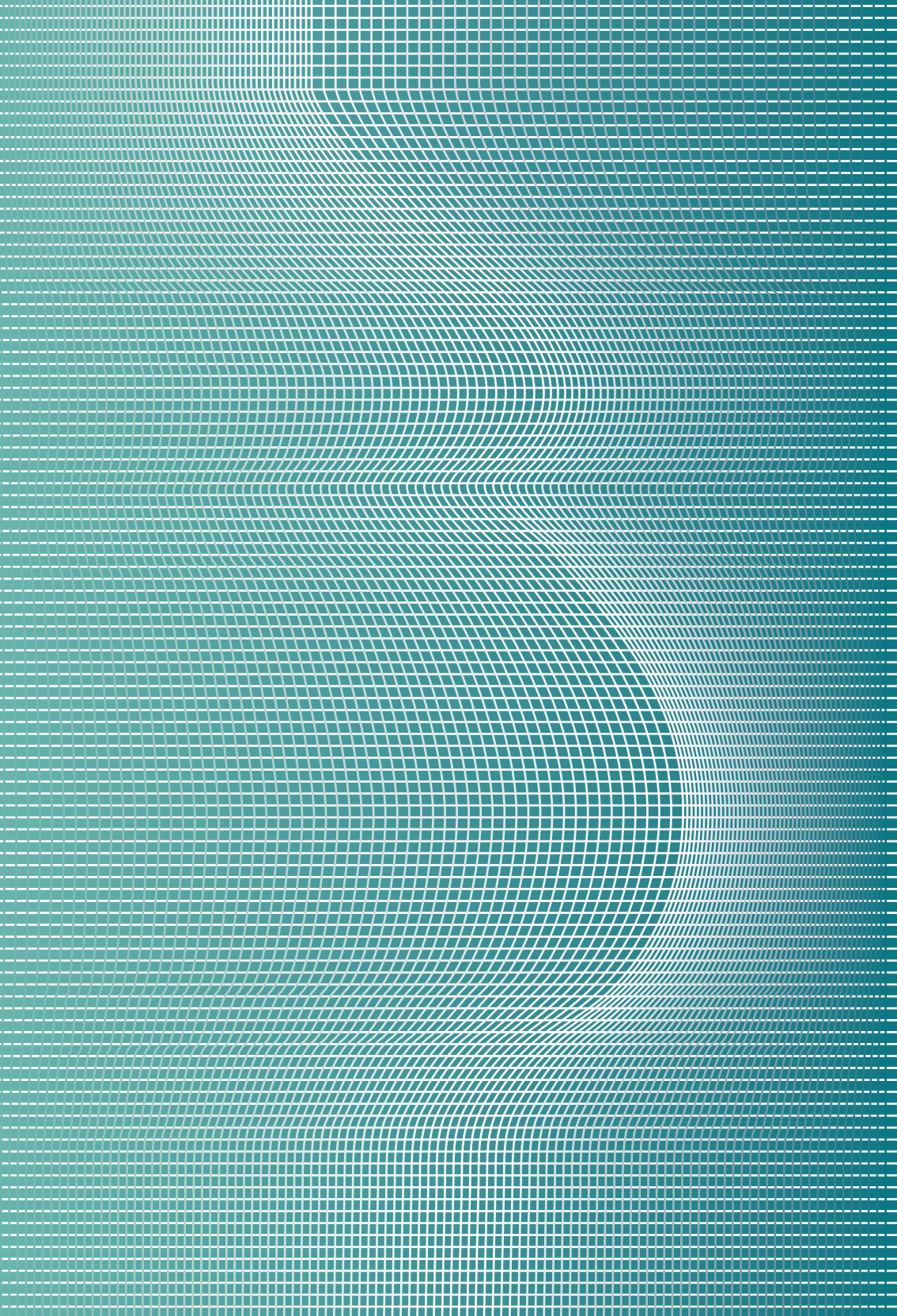
	Valve type N (%)		
	Biological PHV	**Mechanical PHV/combined**	
Women with completed pregnancies	**36 (78%)**	**10 (22%)**	
Completed pregnancies	59 (76%)	19 (24%)	
Median timing of delivery, wks. + days (IQR)	38 +6 (38-40)	39 (36-40)	n.s.
Pregnancies with sufficient obstetric outcome data	44 (75%)	18 (95%)	
Pregnancies with cardiovascular complications	*7 (12%)*	*6 (32%)*	***P<.05***
Pregnancies with cardiovascular complications not (related to) PHV thrombosis	*7 (12%)*	*3 (16%)*	***P=.6***
Heart failure	2 (3%)	2 (9%)	
S(VT) *	4 (7%)	2 (10%)	
PHV thrombosis	0	3 (16%)	***P<.02***
Systemic arterial embolus	0	1 (5%)	
Aortic dissection	0	1 (5%) **	
Structural valve failure	2 (3%) ***	0	
IC/CCU admission	1 (2%)	2 (11%)	
Pregnancies with primary obstetric complications	*26 (59%)*	*16 (89%)*	***P=.02***
Assisted vaginal delivery	8 (18%)	2 (11%)	
CS all	7 (16%)	9 (50%)	**P<.02**
Planned CS	4 (9%)	5 (27%)	P=.1
Emergency CS	3 (15%)	4 (22%)	P=.09
PIH	4 (9%)	0	P>.6
Pre-Eclampsia	5 (11%)	1 (6%)	P>.6
all hypertensive disorders	9 (20%)	1 (6%)	P>.2
PPH	10 (22%)	9 (50%)	**P<.02**
Premature rupture of membranes	2 (5%)	0	
Pregnancies with general complications			
Hospitalization > 1 night, not only for delivery	21 (36%)	10 (53%)	.29
Hospitalization for infection	4 (7%)	2 (11%)	
Haemorrhage (not PPH)	0	2 (11%)****	P=.057
Anaemia	6 (14%)	8 (50%)	**P=.01**
Pregnancies with sufficient *foetal/neonatal* outcome data	47 (80%)	18 (95%)	
Mean birth weight in grams (SD)	*3045 (704)*	*2704 (661)*	*p=.09*
Pregnancies with foetal/neonatal complications	*16 (34%)*	*11 (61%)*	***p<.05***
NRDS	0	1 (6%)	
Infection	2_a (4%)	1 (6%)	
NICU	1 (2%)	2 (13%)	
Prematurity	7_e (15%)	6 (33%)	P=.09
CHD	2 (4%)	0	
Other congenital disease	1 (2%)	2 (12%)	
SGA	6_a (13%)	7 (37%)	**P<.05**
LBW	8_e (17%)	7 (41%)	**P<.05**
Apgar ≤ 7	2 (5%)	1 (7%)	

CHD = congenital heart disease, CS = Caesarean section, IC/CCU= intensive care/coronary care unit, LBW = low birth weight, NICU = neonatal intensive care admission >1 day, NRDS = neonatal respiratory distress syndrome, PHV= prosthetic heart valve(s), PIH= pregnancy induced hypertension, PPH= post-partum haemorrhage, SD = Standard deviation, SGA = small for gestational age, (S) VT = (supra) ventricular tachycardia. * History of pre-pregnancy arrhythmias in n=4 (including 2 women with biological PHV who had a combined SVT and VT) ** in a woman with Marfan syndrome *** 1 unknown brand, 9 years after PHV placement, 1 Carpentier Edwards 5 years after implantation. **** two pregnancies in the same woman. $_e$ = including 2 children out of a triplet pregnancy, $_e$ = including triplet. Apgar ≤ 7 defined as at 1and 5 minutes. Missing data concerning primary obstetrical and foetal/neonatal complications were excluded for analysis.

Table 3. Anticoagulation regimes and complications during pregnancy in women with mechanical PHV.

Woman	Year of pregnancy	PHV location	Anticoagulation regime	Cardiovascular complications	Obstetric complications	Foetal/neonatal complications
1	2010	PVR + AVR	Regime 1. Xa +, range unknown	No	PPH, anaemia, 1 wk. post-partum haemorrhagic shock due to rupture of varix	Prematurity, LBW, SGA*
2	2001	AVR + MVR	Regime 1. Xa -	No	PPH, anaemia, induction of labour	No
	2004	AVR + MVR	Regime 1. Xa -	No	PPH, anaemia	No
	2006	AVR + MVR	Regime 1. Xa -	HF, SVT (CCU)	PPH, anaemia, induction of labour	No
3	2007	PVR	Regime 2, low dose VKA	No	Emergency CS for foetal indication	LBW SGA
	2010	PVR	Regime 2, low dose VKA	Post-partum PHV thrombosis	Planned CS, PPH (shock), anaemia	Prematurity, SGA, LBW, NRDS (infection)
4	1991	AVR	Regime 3	No	PPH, induction of labour, use of forceps	No
	1995	AVR	Regime 2 **	No	Induction of labour	LBW, SGA
5	2005	AVR	Regime 1. Xa -	No	No	No
6	2006	AVR	Regime 3. Xa + range 0,24-0,92 U/l	Systemic arterial thrombosis, PHV thrombosis *(3 times)*	Planned CS for maternal cardiac complication	Prematurity, LBW
7	1994	AVR	Regime 3, combined with TAI throughout	Haemorrhage in 2nd trimester	Use of vacuum extractor	LBW, SGA, Apgar <7
	1996	AVR	Regime 4, combined with TAI throughout	Haemorrhage in 2nd trimester	PPH, anaemia	No
8	1996	*PVR* + AVR	Unknown	No	Emergency CS for foetal indication, PPH, anaemia	SGA
	1998	*PVR* + AVR	Unknown	SVT	Planned CS	SGA
	2005	Ross, AVR + PVR + MVR	Regime 1. Xa -	No	Planned CS	No
	2010	Ross, AVR + PVR + MVR	Regime 5, Xa-	PHV thrombosis in 18th week, HF	Emergency CS for pre-eclampsia, PPH, anaemia	Prematurity
9	2005	AVR	Regime 6, Xa range 0,20-1,47 U/l	No	Unknown	Unknown
10	1998	AVR	Regime 6, Xa -	No	Planned CS	Prematurity, LBW
	2001	AVR	Regime 6, Xa -	Aortic dissection	Emergency CS for maternal cardiac complication	Prematurity

Additional biological PHV are presented in italics. Anticoagulation regimes are sorted according to anticoagulation used in 1st trimester, 2nd trimester, 3rd trimester and around delivery. **Regime 1:** VKA, LMWH, VKA, LMWH; **Regime 2:** Vitamin K antagonists (VKA) throughout, Heparin intravenous (iv) around delivery; **Regime 3:** VKA, Heparin subcutaneous (sc), VKA, Heparin iv; **Regime 4:** Heparin iv, Heparin sc, VKA, Heparin iv; **Regime 5:** VKA, LMWH, VKA, Heparin iv; **Regime 6:** Low molecular weight heparin (LMWH) throughout (early switch from VKA to LMWH); AVR = aortic valve replacement, CCU = coronary care unit admission, CS= Caesarean section, HF = heart failure, MVR = mitral valve replacement, NRDS = neonatal respiratory distress syndrome, PHV = prosthetic heart valve(s), PPH= post-partum haemorrhage, PVR = pulmonic valve replacement, SGA = small for gestational age, SVT = supraventricular tachycardia, TAI = thrombocyte aggregation inhibitor; Prematurity is defined as delivery <37 weeks. *This child had congenital metabolic disease, **presented in 18th week of pregnancy.



8

Efficacy and safety of direct oral anticoagulants during pregnancy; a systematic literature review

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Thromb Res. 2018 Jul 19;169:123-127. doi: 10.1016/j.thromres.2018.07.022.

ABSTRACT

Introduction

Direct oral anticoagulants (DOACs) are increasingly used for anticoagulation or prevention of thromboembolic events in conditions that may co-occur with pregnancy. However, evidence regarding efficacy and safety during pregnancy is scarce.

Aim

To review the current literature concerning the efficacy, safety and outcome of DOACs during pregnancy in humans.

Methods

We systematically searched the MedLine public database for all studies describing the use of DOACs during pregnancy published up to July 4th 2017.

Results

236 cases of DOAC use during pregnancy were reported. Rivaroxaban was the most reported DOAC (n=178). DOACs were mostly used for prophylaxis or treatment of venous thromboembolism (n=91). DOACs were discontinued within the first 2 months of pregnancy in 84%, maximum reported duration of use was 26 weeks. Pregnancy outcome data were available for 140 pregnancies. Thirty-nine pregnancies were electively terminated. In the remaining 101 pregnancies total miscarriage rate was 31% (n=31) and live birth rate was 68% (n=69, 1 missing). Foetal and neonatal abnormalities were reported in 8 pregnancies, of which at least half were suspected to be related to rivaroxaban use during the 1st trimester of pregnancy. In only 18% of cases (n=42), the presence or absence of thrombotic and bleeding complications was reported.

Conclusion

The limited available evidence raises concern regarding embryo-foetal safety, with high incidence of miscarriages and at least a 4% rate of anomalies with the use of rivaroxaban. Not enough data are available to judge safety and efficacy of the use of DOACs during pregnancy.

INTRODUCTION

Direct oral anticoagulants (DOACs) are increasingly used as anticoagulation treatment in patients with atrial fibrillation (AF), deep venous thrombosis (DVT) and pulmonary embolism (PE).[1 2] Pregnancy is a known risk factor for both DVT and PE.[3] Moreover, in women of fertile age with heart disease, atrial fibrillation is a common rhythm disorder that may warrant anticoagulation therapy. Earlier studies have shown that anticoagulation with the use of vitamin K antagonist can cause serious foetal malformations, especially when used in higher dosages between 6-12 weeks of pregnancy.[4-7] Low molecular weight heparins (LMWH) appear safe for the foetus as they do not cross the placenta, however, maternal anticoagulation may be suboptimal and the adequate methods and intervals for monitoring (via anti Xa blood sample measurements) is still discussed.[4 6 8] Furthermore, LMWH are administered by daily injection, which causes pain as well as other complications such as injection infiltrates and hematoma. A direct oral alternative exists: the DOAC. While DOACs are increasingly used for anticoagulation purposes outside pregnancy, their efficacy and safety during pregnancy is unknown due to exclusion of pregnant women in DOAC study protocols and current guidelines advise against DOAC use during pregnancy. Because pregnancy is a dynamic hypercoagulative state, the effectiveness of anticoagulation medication may not be adequate during pregnancy.

Additionally, the direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban are partly, and dabigatran mainly, eliminated by the kidneys. Given the markedly increase of glomerular filtration rate during pregnancy, anticoagulation with DOACs at regular dosages may be insufficient due to increased renal elimination, as has previously been reported with the use of low molecular weight heparins (LMWH).[9 10]

Furthermore, dabigatran inhibits clot formation by direct inhibition of factor IIa, thus decreasing the transition of fibrinogen into fibrin. During pregnancy fibrinogen levels are elevated, which is another reason that dabigatran, as well as other DOAC dosages could be insufficient in pregnant women.[11] Women who use LMWH during pregnancy are currently monitored and dose-adjusted by anti-Xa measurements.[6] Whether or not dose adjustment according to anti-Xa levels is useful for DOAC use, including pregnant women, is yet unknown.

Furthermore, an antidote for dabigatran is commercially available but antidotes for the Xa inhibitors are still in the stage of clinical trial. Treatment of bleeding complications during pregnancy and delivery can therefore theoretically be challenging. Additionally, dabigatran, rivaroxaban and edoxaban, have been shown to cross the placenta in perfusion models. Therefore toxic effects on the foetus may possibly be a complication of the use of DOACs during pregnancy.[12 13]

To update current knowledge and evaluate the use of DOACs during pregnancy we systematically reviewed the current literature concerning the efficacy, safety and pregnancy outcome of the use of DOACs in pregnant patients.

METHODS

We systematically searched the *PubMed/MedLine public database* for all studies dated up to 04-07-2017. Search terminology was: (((((("Dabigatran"[Mesh]) OR "Rivaroxaban"[Mesh]) OR "edoxaban" [Supplementary Concept]) OR "apixaban" [Supplementary Concept]) OR "ximelagatran" [Supplementary Concept]) AND "Pregnancy"[Mesh]; Dabigatran AND pregnancy; Rivaroxaban AND pregnancy; Apixaban AND pregnancy; Edoxaban AND pregnancy; Ximelagatran AND pregnancy; ((Direct oral anticoagulants) OR DOAC) AND pregnancy; ((New oral anticoagulants) OR NOAC) AND pregnancy. We included all studies and study designs which reported the use of DOAC during pregnancy or within 1 month post-partum. We excluded studies not discussing DOAC use during pregnancy and guidelines or reviews when they did not report new cases or data. Studies could be included via cross-referencing. Duplicates were electronically removed.

Collected data were type of DOAC and indication, timing of use during pregnancy, any described thrombotic complications, any described bleeding complications, and pregnancy outcome including occurrence of anomalies.

RESULTS

For inclusion, see figure 1. Six articles were included, of which 2 larger studies, with overlap in outcome data, and 4 case reports, presented in table 1. All studies were recently performed (2014-2016). Overall, the use of DOACs during pregnancy was reported in 276 cases of which 40 were double reported, resulting in 236 reported cases for analysis. Rivaroxaban was the most reported DOAC (n=178, 75%), followed by dabigatran (n=27, 11%), apixaban (n=21, 9%) and edoxaban (n=10, 4%). Indication for DOAC use was reported in 97 cases (41%). Reported indications were prophylaxis or treatment of DVT (n=91, 94%), AF (n=4, 4%), PE (n=1, 1%) and congenital thrombophilia (n=1, 1%).

Timing of discontinuation of the DOAC during pregnancy was known for 73 pregnancies (31% of total reported cases). In these pregnancies, DOACs were discontinued within the first 2 months of pregnancy in 61 women (84%), see table 2. The maximum reported duration of DOAC use during pregnancy was 26 weeks.[14]

Pregnancy outcomes were reported in 140 pregnancies (59%), and are reported in table 2. Of these pregnancies, 28% were electively terminated. Two studies reported the reasons for the elective terminations. In one study 8 elective terminations were observed; 6 for social reasons, 1 for fear of malformations and 1 for a complex foetal heart defect in a woman who previously had an electively terminated pregnancy for foetal heart defects while not using a DOAC.[14] The other study reported 13 known indications for 39 elective terminations, of which 7 for a social indication, 3 for fear of malformations, and 3 for non-DOAC related medical reasons.[15] For ongoing pregnancies, the miscarriage rate was 31% (ranging 14-44%), overall live birth rate was 68% (ranging 50-86%). There were no perinatal deaths.

The presence or absence of thrombotic and bleeding complications were reported for 42 pregnancies (18%) and consisted of 2 thrombotic complications (PE (n=1), DVT (n=1), 5%). Caesarean section occurred in 10 pregnancies, and bleeding post-partum or post abortion in 3 pregnancies (8%, including the woman who used a DOAC during the post-partum period). In two pregnancies, thrombocytopenia was reported.

Foetal and neonatal abnormalities were reported in 8 pregnancies in which rivaroxaban was used (8% of the 105 pregnancies with rivaroxaban use with sufficient data reported), during the 1st trimester of pregnancy. For details of reported abnormalities see table 3. Of these, 4 (4%) are possibly related to the rivaroxaban use.[16] No foetal and neonatal abnormalities were reported for other DOACs.

DISCUSSION

We reviewed two hundred and thirty six cases of DOAC use during pregnancy that were reported in recent literature (2014-2016). The data suggest a high miscarriage rate compared with a 20% miscarriage rate in the general population and raise concern about a possible association with foetal anomalies.[17]

Outcomes of pregnancies were only available in 59%. Elective terminations were performed in 28% of the pregnancies with sufficient outcome data. However, only once an elective termination was performed because of an anomaly and in this case a relation with the DOAC was unlikely. Reasons for elective terminations were underreported. The most reported reason for termination was a social indication. The high rate of termination for a social reason is understandable because patients with DOACs were probably advised against pregnancy, therefore their pregnancies might already were unplanned/unwanted in the first place. Fear for malformations was also reported and may have hypothetically also played a role in the cases with unknown reason for elective termination.

High miscarriage rate (31%) was observed in ongoing pregnancies. Increased miscarriage rate in animals using DOACs during pregnancy was previously reported by the United States Federal Drug Administration (FDA) and the European Medicines Agency (EMA) (table 4).[18 19] The high miscarriage rate both in animals and humans may be related to embryonic/foetal toxicity of DOACs. Moreover the bone and facial abnormalities observed in 4% of pregnancies during the use of rivaroxaban raises further concerns about foetal safety. Notably, this percentage may even be an underestimation because most women (84%) discontinued DOAC use within the first 2 months, before anomalies may have developed. The 4% cases that were possibly related to rivaroxaban use are comparable to the anomalies found in animal studies reported by the FDA and EMA (table 4).[18 19] Interestingly, in 3 cases structural bone or facial abnormalities were observed. Whether or not the growth retardation in one other case might also be related to DOAC use remains undetermined. Human and animal data suggest that bone structure formation is possibly affected by the use of DOACs during pregnancy, as is also observed with the use of vitamin K antagonists during pregnancy.[20] No anomalies were reported with the use of other DOACs (other than Rivaroxaban) during pregnancy, but this may well be related to the smaller patient cohorts.

Thrombotic and bleeding complications were highly underreported, and no firm conclusions about their incidence can be made. However, the current data do not raise concern regarding bleeding complications since the percentage of bleeding complications is comparable to other studies with anticoagulation use during pregnancy.[21 22]

LIMITATIONS

The quality of our systematic review was limited by absence of high quality and randomised studies, small sample sizes, incomplete data and the probability of reporting and publication bias.

CONCLUSION

Safety and efficacy of the use of DOACs during pregnancy is not supported by current literature. The limited available evidence raises concern regarding embryo-foetal safety, because of a high incidence of miscarriages and a 4% rate of anomalies with the use of rivaroxaban. The current limited evidence justifies avoidance of DOACs in pregnant women. For most indications a switch to low molecular weight heparin will be appropriate while, depending on indication, dosage, and stage of pregnancy, vitamin K antagonists may also be used according to current guidelines.[1 23]

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TABLES AND FIGURES

Table 1. Current literature describing the use of direct oral anticoagulants (DOACs) during pregnancy or in the postpartum period.

Study and Year	Type of study	DOAC type	DOAC indication	Missing data	Remarks
Beyer-Westendorf et al. 2016[15]	Combined analysis of: - Review of 2 studies (n=40)[14 24] - FDA cases (n=2) - Cohort of 4 pharmacovigilance databases (n=301) - Case series (n=15) After correction for double inclusion: n=233	Rivaroxaban (n= 176) Dabigatran (n=26) Apixiban (n= 21) Edoxaban (n= 10)	DVT (n=86) DVT Prophylaxis (n=4) AF (n=4)	DOAC indication n=135 (58%) Missing outcome data n=96 (41%)	Overlap with 2 other studies[14 24] Pooled analysis of different DOACs Possible reporting bias by including data from manufacturers
Hoeltzenbein et al. 2016[14]	Pharmacovigilance database survey: Prospective cohort (n=37) Retrospective case series (n=2)	Rivaroxaban	DVT (n=35) AF (n=1)	DOAC indication n=3 (8%)	Data included in study of Beyer-Westendorf[15]
Konigsbrugge et al. 2014[24]	Case report (n=1)	Rivaroxaban	Recurrent DVT and PE		Data included in study of Beyer-Westendorf[15]
Myers et al. 2016[25]	Case report (n=1)	Rivaroxaban	PE pre-pregnancy		
Rudd et al. 2015[26]	Case report (n=1)	Rivaroxaban	DVT post-partum		
Vausse et al. 2016[27]	Prospective cohort study, with DOAC case (n=1)	Dabigatran (n=1)		DOAC indication (n=1)	Cohort of women with prosthetic heart valves, indication DOAC unclear

AF = atrial fibrillation, DVT = deep venous thrombosis, LOE = level of evidence, PE = pulmonary embolism.

Table 2. Outcomes of pregnancies with sufficient outcome data in the current literature in women who use a DOAC during pregnancy.

	All DOACs[14] [15 24-27]	**Rivaroxaban** [14 15 24-26]	**Dabigatran**[1] [5 27]	**Apixaban**[15]	**Edoxaban**[15]
Pregnancies with sufficient outcome data (n,% of all pregnancies)	140 (59%)	105 (59%)	13(48%)	12 (57%)	10 (100%)
Cases with known duration of exposure (n, %)	73 (52%)	*	*	*	*
Maximum duration of exposure	1 month (n=22) 2 months (n=39) 3 months (n=2) 4 months (n=3) 5 months (n=3) 6 months (n=1)	* 1 week (n=1) 10 weeks (n=36) 15 weeks (n=1) 25 weeks (n=1) 26 weeks (n=1) Post-partum (n=1)	* 10 weeks (n=1)	*	*
Elective abortion (n,%)	39 (28%)	26 (25%)	7 (54%)	3 (25%)	3 (30%)
Ongoing pregnancies (n, %)	101 (72%)	79 (75%)	6 (46%)	9 (75%)	7 (70%)
Missing offspring outcome (n,%) **	1 (1%)	0	1 (17%)	0	0
Live birth (n,%) **	69 (68%)	55 (69%)	3 (50%)	5 (56%)	6 (86%)
Miscarriage (n,%) **	31 (31%)	24 (30%)	2 (33%)	4 (44%)	1 (14%)
Perinatal death (n,%) **	0	0	0	0	0

DOAC = direct oral anticoagulant. * incomplete or unknown because of pooled analysis of all DOACs in the study of Beyer-Westendorf.15 ** Elective abortions excluded to demonstrate the natural course of ongoing pregnancies in women with DOAC use during pregnancy.

Table 3. Abnormalities reported as possibly associated with the use of Rivaroxaban during pregnancy.

Study	**Trimester of Rivaroxaban use**	**Pregnancy outcome**	**Abnormality**	WHO-UMC causality category[16]
Beyer-Westendorf et al.[15]	1st	Live birth	Renal pelvis dilatation	Unlikely
			Facial dimorphism	Possible
	1st	Live birth	Mild hip dysplasia	Possible
	1st	Live birth	Septum pellucid cyst	Unlikely
	1st	Miscarriage	Anhydramnios	Unlikely
	1st	Miscarriage	Intra-uterine growth retardation	Possible
Hoeltzenbein et al.[14] Beyer-Westendorf et al.[15]	1st	Elective termination	Complex foetal heart defect	Unlikely
	1st	Miscarriage	Abnormal limbs ('crumpled')	Possible

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	1st	Live birth	Mild hip dysplasia	Possible
	1st	Live birth	Septum pellucid cyst	Unlikely
	1st	Miscarriage	Anhydramnios	Unlikely
	1st	Miscarriage	Intra-uterine growth retardation	Possible
Hoeltzenbein et al.[14] Beyer-Westendorf et al.[15]	1st	Elective termination	Complex foetal heart defect	Unlikely
	1st	Miscarriage	Abnormal limbs ('crumpled')	Possible

Table 4. United States Federal Drug Administration (FDA) and European Medicines Agency (EMA) information on embryo-foetal toxicity in female animals using DOACs during pregnancy (no human studies available).

DOAC*	FDA pregnancy category (animals only)	FDA and EMA information on embryo-foetal toxicity in animal studies[18 19]
Rivaroxaban	C	At clinically relevant plasma concentrations. – *post-implantation loss* – *retarded/progressed ossification* – hepatic multiple light coloured spots – increased incidence of common malformations – placental changes At 4x human exposure dose: – *increased resorptions* – decreased number of live foetuses – *decreased foetal body weight*
Apixaban	B	No increased risk
Edoxaban	C	At 20-65x human exposure dose: – increased post-implantation loss – increased spontaneous abortion – decreased live foetuses – decreased foetal weight – absent or small foetal gallbladder
Dabigatran	C	At 2.6-4.6 x human exposure dose: – increased pregnancy loss – increased the number of dead offspring – increased incidence of delayed or irregular ossification of skull bones and vertebrae At 13.3x human exposure dose: – increased incidence of resorptions – decrease in viable foetuses – decrease in foetal weight

Abnormalities corresponding to abnormalities found in human foetuses in our review are presented in Italics. DOAC = direct oral anticoagulant. * Ximelagatran is not EMA and FDA approved and therefore not described.

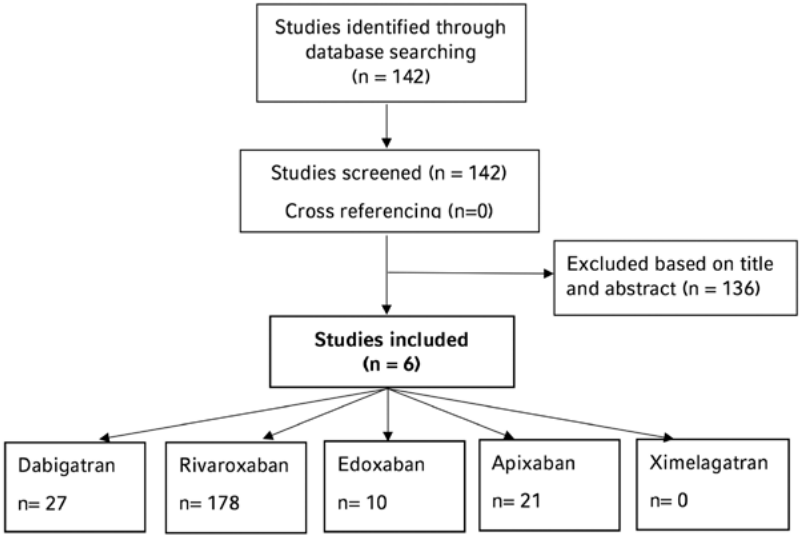
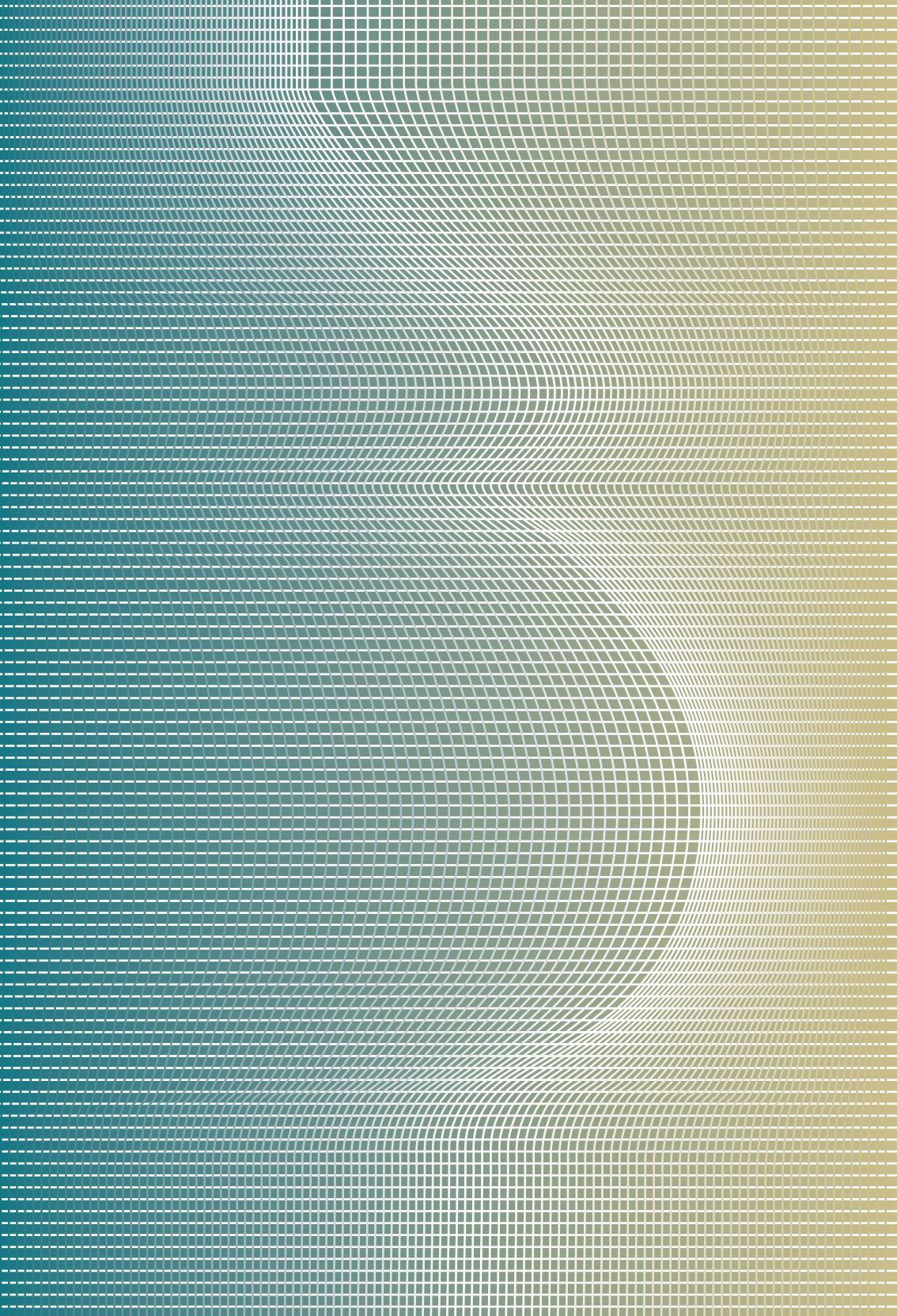


Figure 1. Inclusion.



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Pregnancy and pulmonary hypertension: a contemporary review

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Best Pract Res Clin Obstet Gynaecol. 2014 May;28(4):579-91. doi: 0.1016/j.bpobgyn.2014.03.003

ABSTRACT

Pulmonary hypertension during pregnancy is associated with considerable risks of maternal mortality and morbidity. Our systematic review of the literature on the use of targeted treatments for pulmonary arterial hypertension during pregnancy indicates a considerable decrease of mortality since a previous review in 1998 (16% v 38%), and a further non-significant decrease in mortality since the latest review in 2009 (16% v 25%). In addition to the use of targeted treatments, the timely institution of these treatments, and early planned delivery, may contribute to better outcome. Furthermore, research suggests that women with mild pulmonary hypertension or favourable functional class may have a better prognosis, but there is yet no proof of decreased mortality among these women. Despite an improved prognosis, pregnancy is contra-indicated in women with pulmonary hypertension and, when pregnancy occurs, termination should be considered. When pregnancy continues, management by a multidisciplinary team in a specialist centre is indicated.

INTRODUCTION

Pulmonary hypertension (PH) is a rare disease with different aetiologies. Despite improvement in treatment options, it still carries a grave prognosis with significant morbidity and mortality. The haemodynamic changes of pregnancy are not well tolerated in women with PH. Mortality has been described in up to 50%.[1] There are indications that the prognosis has improved in recent years, but pregnancy is still regarded contraindicated in women with PH.[2 3] The purpose of this article is to give a brief overview of the diagnosis, classification and pathophysiology of PH as well as of modern treatment options and to summarize the available literature regarding pregnancy in women with PH. Our specific aims are to describe determinants of the prognosis of pregnant women with PH. We systematically review the literature describing the outcome of pregnancy in women treated with targeted PH pregnancies.

Definition, classification and pathology of PH

PH is defined as an increase in mean pulmonary arterial pressure (mPAP)) ≥ 25 mm Hg at rest as assessed by right heart catheterization.[4] At the fourth World Symposium on Pulmonary Hypertension in Dana Point (2008) a clinical classification of PH was agreed upon, which is summarized in table 1 and which is incorporated in the European Guidelines.[4] Haemodynamically, PH associated with left heart diseases (group 2) can be characterized as post-capillary PH with pulmonary capillary wedge pressure > 15 mm Hg. All other groups (groups 1,3,4,5) are defined as pre-capillary PH, in these conditions pulmonary capillary wedge pressure is ≤ 15 mm Hg. In patients with PH cardiac output can be normal or reduced. It is useful to realize that pulmonary hypertension comprises all patients with increased mPAP ≥ 25 mm Hg at rest, while the term pulmonary arterial hypertension (PAH) is reserved for the clinical condition of group 1 PH (table 1).

The pathophysiology differs between the clinical groups. In group 1 (PAH) the distal pulmonary arteries show intimal proliferation, medial hypertrophy, inflammatory and thrombotic lesions, as well as complex plexiform lesions. Pulmonary veins are only affected in group 1. The increase in pulmonary vascular resistance (PVR) is the result of multiple contributing factors. These include vasoconstriction resulting from an imbalance of vasodilator and vasoconstrictor substances associated with endothelial dysfunction, as well as inflammation, proliferation and thrombosis. In group 2 (PH due to left heart disease), the backward transmission of the elevated left atrial pressure leads to an increase in capillary wedge pressure and mPAP. The pulmonary veins are enlarged and thickened, interstitial oedema is observed and intimal fibrosis and medial hypertrophy may occur. When the mPAP is disproportionally elevated compared to the capillary wedge pressure (increased transpulmonary gradient) the PVR will also be increased. Reversible vasoconstrictive or fixed obstructive

PH can be present. Group 3 (PH due to lung diseases and hypoxia) is characterized by vasoconstriction reactive to hypoxia as well as by inflammation, while toxic effects of smoke and mechanical effects (emphysema) may play a role. Loss of capillaries is demonstrated. Medial hypertrophy and obstruction of distal arteries due to intimal proliferation are aspects of the pathobiology.

Group 4 (chronic thrombo-embolic PH) is characterized by organized thrombi leading to pulmonary arterial stenosis or occlusion. Coagulation abnormalities may play a role in the pathogenesis of thormbo-embolic PH. Local thrombosis can occur. In non-obstructed areas abnormalities indistinguishable from the lesions found in PAH are found.

Group 5 is a heterogeneous group and the pathobiology and physiology is not well defined.[4]

Haemodynamic and haemostatic changes in the pregnant PH patient

Early in pregnancy plasma volume starts to increase, at the end of the second trimester a raise of 40% in plasma volume is achieved. Red blood cell mass increases by 20-30%. Systemic vascular resistance decreases. As a result of these changes, cardiac output increases. In normal pregnancy, this is achieved mainly by an increase in stroke volume in the first and second trimester, while later in pregnancy heart rate also increases and contributes to the increase in cardiac output. During delivery and postpartum there is a further increase in cardiac output and blood volume caused by pain, anxiety and volume shifts including auto transfusion during uterus contractions.[2] In healthy women, the pulmonary circulation adapts to the increases in blood volume and cardiac output by pulmonary vasodilatation, preventing pulmonary pressures to rise during pregnancy. However, in women with PH the pulmonary circulation is unable to cope with the haemodynamic changes as a result of pulmonary vascular remodelling. Therefore, pulmonary pressures will rise when cardiac output increases. Moreover, the right ventricle may not be able to sufficiently increase cardiac output, and dyspnoea, heart failure and syncope may occur. PH is not uncommonly a new diagnosis during pregnancy since the haemodynamic burden of pregnancy can provoke symptoms that were previously not present. In women with Eisenmenger syndrome, the combination of fixed pulmonary vascular resistance and decrease of systemic vascular resistance leads to increased right-to-left shunt and hypoxia.[5]

Pregnancy is a hypercoagulatory state due to increase in platelet aggregation, increase in concentration of fibrinogen and clotting factors and impairment of venous return by the enlarged uterus. This may result in enhancement of pulmonary vascular thrombosis, as well as peripheral venous thrombosis with risk of pulmonary embolism, further aggravating or causing PH during pregnancy.

Patients with Eisenmenger syndrome, who have an intracardiac right-to-left shunt, are at increased risk of paradoxical emboli during pregnancy. This patient group does not only have hypercoagulation, but bleeding risk is also elevated.

Maternal pregnancy outcome

Despite the well-recognized risk of pregnancy, PH could not be identified as a predictor of maternal outcome in two large studies on pregnancy outcome in women with underlying heart disease.[6 7] This can be explained by the low prevalence of PH in these two studies that were carried out in western countries. PH is a rare condition in women of fertile age and women with PH in these countries are generally advised against pregnancy. In a Korean study on pregnancy in women with congenital heart disease, PH was an independent predictor of maternal as well as of offspring outcome.[8] Pulmonary hypertension predicted the occurrence of heart failure during pregnancy in the European Registry on Pregnancy and Cardiac Disease (ROPAC).[9]

Two previous systematic reviews described the outcome of pregnant women with PH. The first review covered the years 1978-1996 and described 125 pregnancies. Maternal mortality was observed in 38% of these pregnancies and was 30% in primary PH, 36% in Eisenmenger syndrome and 56% in other causes of PH.[1] The second review was published in 2009, it covered the years 1997-2007 and included 73 pregnancies. Maternal mortality was 25%, which was significantly lower than in the previous era (p=0.047). Women with idiopathic PAH had a mortality of 17%, mortality in women with CHD –related PH was 28%, and in women with other causes of PH it was 33%.[3] The majority of deaths occurred after delivery in both reviews. Causes of death were right ventricular failure, sudden death and pulmonary thrombo-embolism. Independent predictors of maternal mortality were late diagnosis and late hospital admission in the early era. In the contemporary review maternal mortality was higher in primigravidae and in women who delivered by caesarean section under general anaesthesia. Importantly, pulmonary pressure was not a predictor of outcome in both reviews. NYHA functional class and the use of advanced PH therapies (which was reported in 73% in the last review) were not found to predict maternal outcome.

NYHA class is however an established predictor of pregnancy outcome in many studies of pregnant women with underlying heart disease.[6-10]

Two series describing a total of 54 pregnancies have been published since the last review, that specifically gave attention to severity of pulmonary hypertension and to functional class and their relation to maternal outcome (table 2).[11 12] It appeared that patients with mild PH (systolic pulmonary artery pressure (SPAP) < 50 mm HG or mPAP < 40 mm Hg) had less increase in PAP during their pregnancies, were more often in NYHA class I or II in early pregnancy

(p<0.0001) and deteriorated less often in NYHA class (p<0.0001). However, a few patients with mild PAH did deteriorate from NYHA class II to class III/IV during pregnancy. Maternal mortality was surprisingly low in these 2 studies (2 of 54 patients, 4%). Both women that died had severe PH. Terminations and miscarriages are excluded from this analysis. In both studies, women with severe PH delivered earlier than women with mild PH. Delivery often was planned earlier in pregnancy based on clinical or haemodynamic deterioration. These planned early deliveries may have contributed to the good outcome. Advanced therapies (prostacyclin analogues, phosphodiesterase inhibitors and endothelin receptor antagonists) were not available for the patients in these 2 series.

A Chinese recent series described 30 pregnancies and reported maternal mortality in 17%. In this series only a few women were treated with targeted PH therapies.[13]

In another recent series describing 20 pregnancies and 6 terminations, unfortunate maternal outcome (death or transplantation) occurred in 4 of the 20 pregnancies (20%).[14] Women who died or required transplantation (n=4) had higher mPAP than patients who survived and delivered healthy babies (n=16) (mPAP 71 ± 5 versus 36 ± 15 mm Hg). Of note, all women that were responders to calcium channel blocker therapy (n=8) had successful pregnancies. These women had nearly normal pulmonary pressures with calcium channel blocker therapy (mPAP 30 ± 6 mm Hg). In these patients calcium channel blocker therapy was continued throughout pregnancy. Several other patients used advanced PH therapies.[14]

In summary, these four recent series seem to confirm an improved prognosis of pregnancy in women with PH. In these series prognosis seems better in women with mild PH, especially when they are in NYHA class I or when they have well-controlled PH with calcium blocker therapy.

Outcome of termination of pregnancy and miscarriage is scarcely described in the literature. A recent prospective series of 26 pregnancies in women with PH included 6 induced abortions, mainly in women with severe PH. There were no complications.[14] Another series included 3 miscarriages at 6-12 weeks of pregnancy, maternal outcome in these women was good.[15]

Current therapeutic strategies in PH

Therapeutic strategies in non-pregnant patients vary with the clinical classification. Anticoagulation therapy is usually prescribed in patients with idiopathic and heritable PAH and PAH associated with anorexigens. It may also be considered in group 1.4 PAH depending on the underlying disease. In patients with portal hypertension or Eisenmenger syndrome the risk of bleeding is often elevated (oesophageal varices, haemoptysis) and the use of anticoagulation therapy is therefore controversial. Anticoagulation therapy is indicated lifelong

in chronic thrombo-embolic PH (group 4).[4] When there is an established indication for anticoagulation therapy outside pregnancy, anticoagulation should be maintained during pregnancy.[2] Vitamin K antagonists are placenta-permeable and are associated with embryopathy with a risk of malformations of on average 6% (dose-dependent) when used in the first trimester, while there is an additional risk of foetal intracranial bleeding throughout pregnancy.[16 17] Low molecular weight and unfractionated heparin do not cross the placenta and therefore can be used relatively safe during pregnancy. They should be monitored and dosed according to anti-factor Xa levels or activated thromboplastin time since dose requirements change considerably during pregnancy.[2] Diuretics are recommended in PH patients when clinical signs of heart failure are present. During pregnancy, the widest experience exists with furosemide and hydrochlorothiazide. Both cross the placenta but are probably not foetotoxic, though data in humans are limited. They may cause placental hypoperfusion and oligohydramnion. Spironolactone is preferably avoided because it is associated with anti-androgenic effects in male animal fetuses.[2]

Current specific therapies for patients with PH are calcium channel blockers, endothelin receptor antagonists, phosphodiesterase inhibitors and prostanoids. Calcium channel blockers are mainly reserved for group 1 (PAH) patients who show a positive response to a vasoreactivity test. For non-responders they are contra-indicated. Furthermore, they are not advised in Eisenmenger syndrome. Vasoreactivity is determined by exposure to nitric oxide, prostanoids or adenosine during right heart catherization. The most widely used calcium channel blocking agents in PAH are nifidepine and diltiazem. During pregnancy, nifedipine is routinely used to treat preterm labour and pre-eclampsia and seems not associated with foetotoxicity when used in the second and third trimester of pregnancy. It is tocolytic and may cause placental hypoperfusion due to hypotension. It is foetotoxic in animals and human data on its use in the first trimester are very scarce. Dilatiazem is foetotoxic in animals and there are no controlled studies in humans. A retrospective review did not reveal important risks for the foetus. Both drugs should only be used in pregnant women when the benefit clearly outweighs the risk. It should be kept in mind that usually higher dosages are used in patients with PH than for other indications. However given the high maternal risk of pregnancy in women with PH, it should be considered to continue these drugs when there is an indication outside pregnancy. Endothelin receptor antagonists (ERAs) exhibit a strong vasodilating and antiproliferative effect by blocking the effect of endothelin-1. The oral ERAs currently in use are bosentan and ambrisentan. They have shown to be beneficial by improving exercise capacity and functional class in PAH group 1. Their use in pregnancy is contra-indicated based on serious teratogenicity in animals. They may decrease the efficacy of hormonal contraceptives. It is advised to use 2 different methods of contraception to ensure that pregnancy does not occur. Phosphodiesterase-5-

inhibitors lead to prolonged vasodilatory effect of nitric oxide in pulmonary arteries. Phosphodiesterase-5-inhibitors not only have impact on pulmonary vascular tone but also have favourable effects on the myocardium since they may block adrenergic hypertrophic and pro-apoptotic signalling. These oral medications have proven efficacy in increasing exercise tolerance, improving functional class and delaying clinical worsening inPAH group 1. Sildenafil and tadalafil are the current agents in use. Sildenafil was not foetotoxic in animal studies, even with high dosages, but human data are scarce. Tadalafil also appeared safe in animal studies. Prostacyclin derivates are pulmonary and systemic vasodilators and inhibit platelet aggregation. Epoprostenol needs to be administered as a continuous intravenous infusion, while treprostinil can also be given subcutaneously or as inhalation therapy. Iloprost is another agent that is administered by inhalation. The short half-life and way and frequency of administration is a disadvantage of these medications. When they are discontinued, for example because of failure of an infusion pump, severe rebound aggravation of PH can occur, especially with epoprostenol. Epoprostenol and iloprost are used in patients with functional class III or IV, treprostinil is also used in functional class II. Clinical benefits of prostacyclin derivates include improvement in mortality, exercise capacity, and functional class. Epoprostenol and treprostinil did not show foetotoxicity or teratogenicity in animal studies but human controlled studies are not available. Iloprost is foetotoxic in animals, human data are scarce. Based on these data, when prostacyclin derivates are indicated during pregnancy, theoretically epoprostenol and treprostinil are favoured over iloprost.[2 4 5]

SYSTEMATIC REVIEW OF TARGETED PH TREATMENT AND PREGNANCY OUTCOME

We performed a systematic review of the literature to analyse the outcome of pregnancy in women with PH who had been treated with targeted PH therapies (calcium channel blockers, nitric oxide, prostacyclin derivates, endothelin receptor antagonists, or phosphodiesterase inhibitors.

Methods

We reviewed the literature concerning the treatment of women with pulmonary arterial hypertension during pregnancy using the guidelines of the PRISMA-statement protocol (available at www. prisma-statement.org). The inclusion procedure is illustrated in figure 1. We performed an extensive MedLine public database search for literature concerning pulmonary (arterial) hypertension and pregnancy, as described in Figure 1. We limited the publication dates from 01-01-1998 up to the date last searched (19-9-2013) to minimize inclusion of obsolete therapies. The filters Humans, Female, Adolescent: 13-18 years, Adult: 19+ years,

Adult: 19-44 years (to include only patients of fertile age) were activated. Based on reviewers' language skills only articles written in Dutch, English and German were included. Duplicates were removed and articles identified through other resources (i.e. cross-referencing) were added. Articles were screened based on abstract and title. Literature not considering pulmonary hypertension in pregnant women was excluded. Subsequently remaining full-text articles were screened and included or excluded (Figure 1). Reasons for exclusion were inadequate endpoints, review article or comment without original cases, no advanced PH therapy, article not available, or inconsistent data. Additionally, 4 publications were excluded because of insufficient individual patient data to allow analysis; these publications have been discussed separately.[11-14] Publication bias and selective reporting within studies could not be minimized. We excluded miscarriages and pregnancy terminations. To allow comparison with previous reviews, we classified PH patients as idiopathic PAH (IPAH)(when no specific cause could be identified), PH associated with congenital heart disease, including Eisenmenger syndrome (CHD-PAH) or PH with other causes (oPH)(PH associated with connective tissue disease, medication, HIV, chronic pulmonary thrombo-embolism).[1 3] PH group 2 and 3 were not included as PAH specific therapy is not indicated for these forms of PH. We collected data on cause of PH, sPAP, mPAP, medication including targeted PH medication, start of PH medication (weeks of pregnancy), time of delivery, mode of delivery, functional class, maternal and foetal death. For comparison with outcomes of previous reviews, Fishers exact test was used. P-values were 2-sided and a p-value of <0.05 was considered significant.

Results

We included 31 studies with 77 parturients who were treated with targeted PH therapies.[15 18-48] Mortality occurred in 12 women (16%). In the IPAH group (N=32) 3 women (9%) died, in the CHD-PAH group (N=30) 7 women (23%) died, mortality in the oPH group (N=15) was 13% (N=2). Details of the women that died are provided in table 3. Most deaths occurred postpartum (N=10, 83%). Two deaths were at 28 weeks of pregnancy and during delivery. Causes of death were known in 10 women, in 7 of them right ventricular failure was involved, one woman died of sepsis, one died suddenly at home, and one died during delivery due to intractable tachycardia after a bolus of oxytocin. Offspring death occurred only in 3 pregnancies (4%), and in 2 of those pregnancies the mother also died. Comparison with the review of Weiss showed a significant decrease in total mortality from 38% to 16%, p=0.0005.[1] Mortality decreased significantly in patients with oPH, but in the subgroups with CHD-PAH and IPAH the decrease in mortality was not significant. There were no significant differences in mortality compared with the review of Bedard and all, but there was significant overlap in inclusion (table 4).[49] Calcium channel blockers were used in 13 women and were the only targeted therapy in 5 of these women. Prostacyclin derivates were the most common used targeted medication (N=61). Sildenafil was given in

26 women and NO inhalation therapy in 10 women. Bosentan was used pre-pregnancy and discontinued in 3 women, 2 women continued this medication throughout pregnancy, 9 women started with bosentan post-pregnancy. More than one targeted PH therapy was used in 30 women (39%). In 65 pregnancies (83%) anticoagulation therapy was given, most often low molecular weight heparin. Thirteen women were only receiving targeted PH therapies during their deliveries and/or postpartum. Six of these women died (46%), compared to 9% in the group of women in which targeted PH therapy was started at least a week before their deliveries (p=0.017). One of the six women that died and had received targeted therapy only at delivery or postpartum, presented at delivery and could therefore not have received earlier therapy. In 70 women the severity of PH was reported, 16 women had mild PH (MPAP ≤ 35 mm Hg or (when MPAP was unknown) SPAP ≤ 50 mm Hg), 54 women had severe PH. One of the women with mild PH died (6%) and 10 women with severe PH died (19%)(NS).

Conclusions

Our data do confirm an ongoing decrease in maternal mortality in all subgroups of pregnant women with PH. Despite this decrease, mortality remains high. Mortality risk is especially high postpartum. Interestingly, mortality has not only decreased in women receiving targeted PH therapies. Recent series reporting the outcome of pregnant women with PH in countries where advanced PH therapies were not available, also documented lower mortality than in previous years.[11-13] Early planned delivery may have contributed to improved outcome in these series. Initiation of targeted PH therapy well before delivery appeared to contribute to favourable outcome in our review. Though on average women with mild PH have less increase in pulmonary pressures during pregnancy compared to women with severe PH and though some studies reported that women with mild PH did better than women with severe PH, mortality was not significantly reduced in women with mild PH in our review. Offspring mortality seems to be related to maternal mortality.

MANAGEMENT OF REPRODUCTIVE ISSUES IN WOMEN WITH PH

Though mortality has decreased over time, it is still high and it is difficult to identify women who have a lower risk. Therefore, in line with current guidelines, all women with established PH should be advised against pregnancy.[2] This also implies that girls and women must be informed about safe and effective contraception.[50] Barrier methods such as condoms, diaphragms and cervical caps, give protection against sexual transmittable diseases and do not have health risks. Their high failure rate with typical use (15-30%) makes them however an inappropriate contraceptive for women with PH. Combined contraceptives containing both oestrogen and progestogen (oral, vaginal

ring (Nuvaring) and transdermal patch) are contra-indicated in women with PH because of their association with thrombo-embolic complications. The progesterone only pill (desogestrel 0,075 mg) is effective but requires excellent compliance. The ethonogestrel-releasing subdermal implant is one of the most effective contraceptives available. Bruising at implantation is an issue in women who use anticoagulant therapy, which should therefore be short-term discontinued. Three-monthly medroxyprogesterone-acetate injections are also effective and safe for women with PH. All progestogen-only contraceptives have the disadvantage of irregular vaginal blood loss. Intra-uterine devices have a low failure rate. Their main disadvantages are heavy bleeding (copper spiral) or irregular bleeding (levenorgestrel-relasing device) and the risk of a vagal reaction at insertion which may be poorly tolerated in women with PH, especially in women with Eisenmenger syndrome. Implantation should therefore take place in hospital.[5 50]

ERAs reduce the effectivity of oral contraceptives, therefore use of an additional contraceptive method is advised.

When women with PH become pregnant, termination of pregnancy is recommended.[2] However, since termination is in itself associated with considerable risks in these women, it needs to be performed in a tertiary centre with involvement of an experienced multidisciplinary team (PH specialist as well as anaesthetist and gynaecologist).

When a woman chooses to continue the pregnancy, it is mandatory that she is immediately referred to an expert PH centre and is treated by a multidisciplinary team starting early in pregnancy. The team should comprise pulmonary hypertension specialists as well as a cardiologist, obstetrician and cardiac anaesthetist who have experience in treating cardiac patients with high-risk pregnancies.[2 5 51] Oxygen therapy has no proven benefit on pregnancy outcome but should be applied when hypoxaemia is observed. Restriction of physical activity is advisable. Anticoagulation therapy is given on an individual basis: when it is indicated outside pregnancy it should be continued, but when there is bleeding risk (Eisenmenger syndrome with risk of haemoptysis, oesophageal varices) the risk may outweigh the benefit. Vitamin K antagonists can be replaced by low molecular weight heparin with monitoring of anti Xa levels, especially in the first trimester and the last month of pregnancy. Heart failure is treated with diuretics. Iron deficiency should be treated, but in patients with Eisenmenger syndrome caution is required. Iron depletion may result in these patients in microcytosis which increases blood viscosity, but on the other hand liberal iron repletion can lead to excessive bone marrow activity in the setting of hypoxaemia, which also may increase viscosity. Targeted PH therapy that was used before pregnancy should be continued. ERAs are however teratogenic

and their replacement by other medication (prostacyclin or sildenafil) is usually recommended.[52] The European Guidelines advise however that ERAs may be continued after counselling the patient about their possible teratogenic effects.[2] Based on current literature it is not possible to give strong recommendations about the optimal timing to start PH targeted therapies in patients who did not previously use them. In many reports the start of medication was at the end of the second trimester or during the third trimester. The literature strongly suggests that use of these therapies only during delivery and postpartum is associated with worse outcome than with an earlier start. Therefore we recommend to initiate these medications on an individual basis, preferably 3 months before delivery since optimal treatment effect may only be reached after 3 months, but earlier when clinically indicated. Good results were described both with inhaled and with intravenous prostacyclin and also with sildenafil. It is very important that medication is continued postpartum for a prolonged period, since maternal deaths can occur several months postpartum. The postpartum medication can include ERAs. Again this should be individualized based on pulmonary pressures and clinical situation.

The literature gives reason to believe that a planned early delivery at 32-34 weeks, before the patient deteriorates, is an important contributor to good outcome.[11 12 42] Later delivery (34-37 weeks) may be possible in completely stable women who have mild PH without further elevation of pulmonary pressures during pregnancy. Vaginal delivery is not contraindicated, however, early timing of delivery is in clinical practice reason for choosing caesarean section in many cases. In the review of Bedard et al, general anaesthesia was associated with worse outcome than epidural/spinal anaesthesia. This may be because patients receiving general anaesthesia had more severe disease, but negative effects of general anaesthesia also include increase of pulmonary pressures and cardiodepression.[3] Probably expert application of epidural or a combination of epidural and spinal anaesthesia is the best option for these patients. During delivery monitoring of haemodynamic (heart rate, blood pressure, oxygen saturation) is required but the benefit of invasive monitoring of PA pressures is debatable.

After delivery, the patient should be observed and treated in a critical care setting for several days and remain hospitalized for at least 2 weeks. After discharge frequent clinical and echocardiographic evaluation is advised, since the months after delivery are a period with increased risk of maternal death.[2 5 51 53]

PRACTICE POINTS

- Pulmonary hypertension in pregnant women is associated with high mortality and morbidity despite significant improvement of prognosis in the last decades
- Women with pulmonary hypertension should be advised against pregnancy
- When women with PH are pregnant and choose to continue their pregnancy, management by a multidisciplinary team in an expert centre is mandatory
- Early institution of targeted PAH therapy and early planned delivery may contribute to improved outcome
- Women with mild PH or favourable functional class may have a better prognosis, but since there is yet no proof of lower mortality, they should still be advised against pregnancy

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** articles of particular interest

TABLES AND FIGURES

Table 1. Clinical classification of pulmonary hypertension.

1.	**Pulmonary arterial hypertension**	
	1.1	Idiopathic
	1.2	Heritable(i.e. BMPR2, ALK1)
	1.3	Drugs and toxins induced (i.e. fenfluramine, amphetamine)
	1.4	Associated with
		- Connective tissue diseases,
		- HIV infection
		- Portal hypertension
		- Congenital heart disease (Eisenmenger syndrome, or associated with moderate systemic to pulmonary shunts, small shunts or corrected congenital heart disease)
		- Schistosomiasis
		- Chronic haemolytic anaemia
	1.5	Persistent pulmonary hypertension of the newborn
	1' Pulmonary veno-occlusive disease / pulmonary capillary haemangiomatosis	
2.	**Pulmonary hypertension due to left heart disease** (systolic or diastolic dysfunction, valvular disease)	
3.	**Pulmonary hypertension due to lung diseases and/or hypoxia** (i.e. chronic obstructive pulmonary disease, interstitial lung diseases, mixed restrictive/obstructive pulmonary disease, high altitude, and others)	
4.	**Chronic thrombo-embolic pulmonary hypertension**	
5.	**Pulmonary hypertension with unclear and/or multifactorial mechanisms** (i.e.c haematological disorders, systemic disorders, metabolic disorders and others)	

Table 2. NYHA class, pulmonary pressures and time of delivery during pregnancy in 2 recent studies (Katsuragi and Subbaliah).[11 12]

	Mild PH	Severe PH
NYHA early - late in pregnancy	N=26	N=28
I - I	19 (73%)	3 (11%)
I - II	3 (12%)	-
II – II	2 (8%)	-
II – III/IV	2 (8%)	21 (75%)
III – III/IV	-	4 (14%)
SPAP mm Hg (Katsuragi)	N = 10	N = 14
Early pregnancy	39.3 ± 6.6	68.2 ± 11.1
Late pregnancy	47.2 ± 9.2	95.8 ± 18.5
SPAP mm Hg (Subbaiah)	N = 16	N = 14
Early pregnancy	40.4 ± 3.6	63.1 ± 7.6
Late pregnancy	41.7 ± 4.1	71.6 ± 7.9
Time of delivery (weeks)		
Katsuragi	N=10	N=14
	36.4 ± 4.0	31.4 ± 2.8p < 0.005
Subbaiah	N = 16	N = 14
	37.3 ± 1.1	34.8 ± 1.7p < 0.05

PH, pulmonary hypertension; NYHA, New York Heart Association; SPAP, systolic pulmonary artery pressure.

Table 3. Women who died during pregnancy.

Patient Study	Aetiology Presentation	SPAP mm Hg	PH Therapy Start	Delivery weeks,mode	Death details	Foetal outcome
Patient 1 Curry 2012.[15]	CHD prepregnancy	104	Iloprost postpartum	26, CS	15 days postpartum	Survived BW 620 g
Patient 2 Curry 2012.[15]	CHD prepregnancy	60	Diltiazem prepregnancy	36, CS	delivery (SVT at oxyt)	Survived BW 2570 g
Patient 3 Easterling 1999.[19]	IPAH 28 weeks	75	Prostacyclin	-	8 hours post diagnosis	Died in utero with mothe
Patient 4 Goodwin 1999.[22]	CHD 36 weeks	90	NO inhalation 36 weeks	36, vaginal	5 days postpartum	Survived BW 2640 g
Patient 5 Lust 1999.[25]	CHD 26 weeks	85	NO inhalation delivery; prostacyclin 2 weeks postp	34, vaginal	3 weeks postpartum	Survived BW 1823 g
Patient 6 Duarte 2013.[28]	CHD -	126	Epoprostenol Week 27	28, CS	6 weeks postpartum	Survived -
Patient 7 Kiely 2010.[42]	IPAH 9 weeks	150	Iloprost iv week 14, inh week 34	34, CS	4 wks postpartum, stopped med	Survived BW 1580 g
Patient 8 Monnery 2001.[43]	IPAH 28 weeks	100	NO inhalation delivery; post-partum inh/iv iloprost	32, CS	2 weeks postpartum	Survived -
Patient 9 McMillan 2002.[44]	oPH 16 weeks	32 (during pregn 80)	NO inhalation delivery	31, CS	<1 day postpartum	Survived BW 1500 g
Patient 10 McMillan 2002.[44]	oPH 7 weeks	55	NO inhalation Prostacyclin iv; Both at delivery	32, CS	<1 day postpartum	Died BW 1860 g
Patient 11 Rosengarten 2012.[47]	CHD	-	Epoprostenol iv; sildenafil, Start unknown*	34, CS	<2 weeks postpartum	Survived -
Patient 12 Rosengarten 2012.[47]	CHD	mPAP 50	Iloprost inhalation, sildenafil; start unknown*	34, CS	< 2 weeks postpartum	Survived -

SPAP=systolic pulmonary artery pressure, PH=pulmonary hypertension, CHD=congenital heart disease, CS=Caesarean section, BW=birth weight, g=gram, SVT=supraventricular tachycardia, oxyt=oxytocin, IPAH=idiopathic pulmonary hypertension, oPH, other cause of pulmonaryhypertension;NO=nitricoxide,iv=intravenous,inh=inhalation,postp=postpartum; pregn= pregnancy. * medication was started during pregnancy and not at delivery.

Table 4. Mortality in patients with PH compared between 3 reviews[1,3]; current review.

	Weiss et al (1978-1996)	Bedard et al (1997-2007)	Current Review (1998-2013)
Total mortality	48/125 (38%)	18/73 (25%)	12/77 (16%)
Mortality, IPAH	8/27 (30%)	5/29 (17%)	3/32 (9%)
Mortality, CHD-PAH	26/73 (36%)	8/29 (28%)	7/30 (23%)
Mortality, oPH	14/25 (56%)	5/15 (33%)	2/15 (13%)

IPAH, idiopathic pulmonary arterial hypertension; CHD-PAH, pulmonary arterial hypertension associated with congenital heart disease; oPH, other cause of pulmonary hypertension.

10

Summary, conclusions and future perspectives

In **chapter 1** we introduced the rationale and the aim of this thesis; to evaluate the specific cardiovascular causes of maternal death in the Netherlands, to identify related factors, and to further specify the pregnancy risk for mother and foetus in specific severe cardiovascular diseases with high maternal morbidity and mortality. Also, we aimed to discuss treatment options with the main focus on anticoagulation treatment. Overall, we aimed to search for possibilities for improvement of pregnancy care in these women and provide recommendations in an attempt to contribute to a reduction of cardiovascular maternal mortality and morbidity

WHAT WE HAVE LEARNED

In the **2nd chapter** of this thesis we raised further awareness to the importance of current research in the field of cardiovascular diseases during pregnancy and the post-partum period, as we discussed maternal mortality due to cardiovascular disease. In this chapter we reviewed 96 maternal deaths over a 21 year period in the Netherlands using an existing systematic national confidential enquiry of maternal deaths published by the Dutch Maternal Mortality Committee. We concluded that maternal cardiovascular mortality rates are low, 2.4/100.000 live born children, in the Netherlands We found that the main causes for maternal cardiovascular death were aortic dissection (n=20, 21%), ischemic heart disease (n=17, 18%), cardiomyopathies (including peripartum cardiomyopathy and myocarditis, n=20, 21%) and (unexplained) sudden death (n=27, 28%). In a significant minority possibly avoidable care factors (attributable to the patient or the health care provided) probably contributed to maternal adverse outcome. These factors were patient-related in 40% (pregnancy against medical advice, underestimation of symptoms) and health care provider related in 60% (no recognition or delay of diagnosis, delay in referral), therefore we concluded that awareness of these factors amongst health care providers is important. In this chapter we made several recommendations based on the lessons taught by this chapter that may contribute to further improvement of care for pregnant women with cardiovascular diseases. We learned that (pre) pregnancy counselling is important; not only in women with known heart disease but also in women who are not known with heart disease but have a first degree family member with cardiomyopathy or acute sudden death. This was reflected by four of the seven women who died due to cardiomyopathy, while they were not known with cardiomyopathy pre-pregnancy.

We learned and recommended to take chest pain during pregnancy seriously. Not all chest pain in pregnant women is caused by reflux of pulmonary embolism. Chest pain or back pain may indicate aortic dissection, and a chest CT should be considered. Especially when hypertension or a family history of connective tissue disorders is present. Also, ischemic heart disease should be

considered in pregnant women with chest pain and an electrocardiogram and cardiac biomarker test should be performed.

Furthermore, we learned that we should monitor women with heart disease closely, especially women with cardiomyopathy and women with a heart valve prosthesis (PHV), which we discussed in more detail in chapter 7. We raised awareness that the post-partum period is a vulnerable period for maternal cardiac death (55% of all maternal deaths): it is not over until it is over. And, last but not least, chapter 2 taught that it is not over when it is over: autopsy should be performed in women who die from unexplained causes during pregnancy or in the post-partum period.

In **chapter 3-6** we dove deeper in to the 3rd most common cause for maternal death: IHD, to evaluate not only maternal mortality, but also maternal and foetal morbidity.

First, in chapter 3 and 4, we discussed new onset IHD, including acute myocardial infarction, during pregnancy or in the post-partum period. In chapter 3 we describe our retrospective cohort study leading to the case presentation of 2 pregnancies in women with new onset IHD during pregnancy. More important, we systematically reviewed the overall (1975-2013) and contemporary (2005-2013) literature concerning IHD presenting during pregnancy or postpartum period, resulting in the evaluation of 146 pregnancies, including 57 contemporary cases (2005-2013). In chapter 4 we present another 2 cases of women presenting with IHD during pregnancy. We concluded, mainly from the data observed in the systematic review, that most women with new onset IHD present with chest pain (95%), during the third trimester or postpartum period (71%). The main causes for IHD during pregnancy are coronary dissection (35%) and, in more recent cases, thrombus and embolism (35%). Risk factors for IHD were usually present and often potentially modifiable (smoking), but may be absent in women with IHD caused by coronary artery dissection. IHD manifesting during pregnancy or the post-partum period has a high maternal complication rate: mortality occurs in 8% (6% in contemporary cases). Furthermore, we found an increased perinatal mortality (4%) and premature birth rate (56%) in women with IHD, which was related to high Caesarean section rate (performed in 57%).

In chapter 5 and 6 we additionally describe pregnancies in women with pre-existent IHD, which we evaluated by a retrospective international multicentre cohort study of 50 pregnancies (chapter 5) and a systematic review of 124 pregnancies in women with pre-existing IHD (chapter 6) The systematic review included 2 larger studies (including the study presented in chapter 5), case series and case reports. We found that these pregnancies are high risk pregnancies with a 1 out of 4 chance of ischemic cardiovascular complications including maternal mortality in 2%. Overall, these women only had a 21% chance of going through

an uncomplicated pregnancy (completed pregnancy without cardiovascular, obstetric or foetal/neonatal complications, n=26). Women with atherosclerosis as underlying pathology appeared at highest risk for ischemic complications. . Obstetric pregnancy complications occurred in 58% of the pregnancies, foetal/neonatal complications in 42%.

In **chapter 7** we discussed pregnancy in women with PHV We already concluded based on chapter 2 that these women should be under tight medical supervision. In chapter 7 we evaluated these pregnancies in more detail, by performing a retrospective multicentre cohort study evaluating pregnancy outcomes in an existing cohort of patients with PHV. We included 52 women who had 102 pregnancies of which 78 pregnancies (46 women) ≥20 weeks duration (59 biological, 19 mechanical PHV). We concluded that these women have a high incidence of cardiovascular, obstetric and foetal/neonatal complications during pregnancy or the post-partum period (overall complication rate 17%). We found a much higher incidence of complications in pregnancies in women with mechanical PHV, compared to biological PHV including cardiovascular complications (12% vs 32%, p<.05), obstetric complications (59% vs 85%, p=.02) and foetal/neonatal complications (34% vs 61%, p<.05). These differences were mainly related to the higher occurrence of PHV thrombosis (16% in women with a mechanical PHV) and bleeding complications (50% of the women with mechanical PHV had post-partum haemorrhage). Furthermore, we found that women with pulmonary mechanical PHV appeared especially at high risk during pregnancy. PHV thrombosis often occurred during periods of inadequate monitoring of anticoagulation or necessary interruption of anticoagulation and therefore may be often potentially preventable. The choice for a biological PHV (with higher re-operation rate) in these young women is therefore not indisputable.

Chapter 7 also contributed to the current search for the right anticoagulation regimes during pregnancy in women with mechanical PHV. We added a significant amount of pregnancies with a combined vitamin K and low molecular weight heparin anticoagulation regime (n=8, 42% of the pregnancies in this study) to current literature, and describe related complications. To add to our conclusions in chapter 2, we suggested that an important part of the tight medical supervision of these women it the meticulous monitoring of anticoagulation in pregnant women that is necessary.

In **chapter 8** we discussed the use and safety of the new Direct Oral Anticoagulants (DOACs) during pregnancy in We performed a systematic review of the current literature describing 236 cases of DOAC use during pregnancy. In 140 cases sufficient pregnancy outcome data were reported. This chapter taught that the safety and efficacy of the use of DOACs during pregnancy is not supported by current literature; foetal and neonatal abnormalities were reported in 8

pregnancies, of which at least half were suspected to be related to rivaroxaban use during the 1st trimester of pregnancy. Therefore the limited available evidence raises concern regarding embryo-foetal safety and we therefore concluded that the current limited evidence justifies avoidance of DOACs in pregnant women.

In the final chapter, **chapter 9** we discussed a serious condition, pulmonary hypertension (PH), by performing a systematic review of the literature on the use of targeted treatments for pulmonary arterial hypertension during pregnancy. While pregnancy is regarded as highly lethal in women with PH, only 1 death due to PH was described in chapter 2, which is likely the result of a very low prevalence of PH in the pregnant population because of current guidelines advising against pregnancy in women with PH.[1] In Chapter 9 we found that PH in pregnant women is still associated with high mortality and morbidity (both 16%) despite significant improvement of prognosis related to new targeted treatment options in the last decades. Therefore, we should continue to advise women with pulmonary hypertension against pregnancy. However, when women with PH are pregnant and choose to continue their pregnancy, management by a multidisciplinary team in an expert centre is mandatory and early institution of targeted PH therapy and early planned delivery may contribute to improved outcome.

WHAT WE SHOULD LEARN: RECOMMENDATIONS FOR FUTURE RESEARCH

Medicine is not gender-neutral, and recognition is key

Currently, gender sensitive medicine has gained increasing attention, both in medical science and in the popular media in the Netherlands. As observed in this thesis, pregnancy can influence cardiovascular disease development and cardiovascular diseases (and anticoagulation therapy for cardiovascular diseases) can influence pregnancy outcome. We should take opportunity of the current interest in gender sensitive medicine to raise awareness of the occurrence of cardiovascular diseases during pregnancy and their high mortality risk. This should not only be taught to cardiologists, but to all medical professionals taking care of pregnant women including obstetricians, general practitioners, midwives and emergency medicine physicians. As an emergency medicine specialist, I am glad to see that current emergency medicine literature acknowledges the role of pregnancy in severe medical conditions, including cardiovascular diseases such as aortic and coronary dissections.[2-4] Current literature mainly focuses on the occurrence and treatment of these conditions, but more attention should be payed to the recognition of these diseases during pregnancy. As in emergency medicine, all starts with clinical recognition.[5 6]

Furthermore, as scientists we are obliged to present and incorporate our gained knowledge not only in medical journals and conferences but also in practical training of other doctors. Gender sensitive medicine including the role of pregnancy and hormones on cardiovascular diseases should be a part of the general training of medical students, cardiologists, gynaecologists, general practitioners and emergency medicine specialists. Also, to my opinion, knowledge about how to improve resuscitation of pregnant women is essential for improving their outcomes and the outcome of their unborn babies, and should be an element of the medical training of any attendant in the primary or emergency care of pregnant women.[7] When emphasizing perimortem Caesarean section in the resuscitation of pregnant women in cardiac arrest, an important role for the emergency medicine physician, as a resuscitationist who is both cardiovascular as well as surgically trained, should be stated.

How to treat (pregnancy related) SCAD

As described in **chapter 2-6**, IHD contributes highly to maternal mortality and morbidity during pregnancy and the post-partum period, and is frequently caused by spontaneous coronary artery dissection (SCAD). The best treatment of SCAD is still debated. Whereas percutaneous coronary intervention is associated with low success rate and high likelihood of complications, coronary artery bypass surgery is often required even for single vessel SCAD. Recurrent ischemic events because of persistent or new spontaneous coronary artery dissection are common, also in the context of pregnancy, as observed in chapter 5 and 6.[4 8] Future research should focus on evaluating the best treatment for (pregnancy related) SCAD.

How to effectively and safely anticoagulate pregnant women

Current guidelines advise an individualized approach to anticoagulation in pregnant women with mechanical PHV. A VKA-LMWH combined regimen is recommended in current American and European guidelines[1 9 10] despite the fact that the number of pregnancies described with this regimen is limited (N=60).[11-13] While our study added a significant number of cases with this regimen, more evidence is needed. This is even more important because a LMWH-only regimen is not the answer; a recent prospective population-based study from the UK reported a high incidence of maternal and foetal/neonatal complications, including 9% maternal mortality and PHV thrombosis in another 16% of the pregnancies in women who were largely anticoagulated with LMWH throughout pregnancy.[13]

Furthermore we should learn how to dose LMWH therapy, and how to monitor dosing. When LMWH is used during pregnancy, the dose usually needs to be increased due to an increased glomerular filtration rate and renal clearance of LMWH. Therefore, current guidelines recommend that LMWH should only be used in women with mechanical PHV when administrated twice daily and

when close monitoring of anti-Xa levels is performed.[1 9 14-17] The optimal range of anti-Xa levels, whether to measure peak or through levels and interval of measurements is still debated.[1 13 14 16] Current European guidelines recommend maintaining peak anti-Xa-levels between 0.8 and 1.2 U/ml, but higher target levels (possibly 1.0-1.2 U/ml) may be necessary. [1 13] No evidence-based advice regarding the frequency of anti-Xa monitoring exists, but experts recommend weekly anti-Xa controls.[1 13] Additionally, the data from a recent study suggest that a higher starting LMWH dose than the usual weight-base recommended dose may be advisable in these pregnant women.[13] Further research should evaluate whether a 2 times dosing regime is the right way to dose, or if the dosing frequency should be 3 times daily at least in some patients.

As we recommended in this thesis, DOACs should currently not be used during pregnancy. However, evidence was scarce, and firm conclusions could not be made. We therefore need more high quality studies regarding the use of DOACs during pregnancy.

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Appendices

- Populaire samenvatting
- Curriculum Vitae
- Curriculum Vitae Nederlands
- Dankwoord

Populaire samenvatting in het Nederlands

Zwangerschap, hart- en vaatziekten, en het nut van dit proefschrift

Hart- en vaatziekten (HVZ) zijn de belangrijkste oorzaak van indirecte moedersterfte in Europa en daarmee ook in Nederland. In Nederland is het zelfs zo dat de moedersterfte aan HVZ van 1993 tot 2005 is gestegen.[1-4] Gelukkig sterft niet elke vrouw aan HVZ, sterker nog, het merendeel (over)leeft met een HVZ. Deze vrouwen en hun (ongeboren) kinderen kunnen hier echter wel last van ondervinden, door gerelateerde complicaties die optreden tijdens de zwangerschap of in het kraambed.[5-7] Er is binnen de medische wetenschap nog maar weinig bekend over het risico en de behandeling van HVZ tijdens de zwangerschap, en het risico voor moeder en kind.[9] We verwachten dat er in de toekomst meer jonge vrouwen een HVZ hebben of krijgen, wanneer zij zwanger worden. Dit omdat risicofactoren (zoals overgewicht en suikerziekte) toenemen.[8] Daarom is het van belang om nú onderzoek te verrichten naar HVZ en hun effect op moeder en ongeboren kind. Met als uiteindelijke doel betere zorg voor deze vrouwen, het voorkomen van moedersterfte en het voorkomen van aan HVZ gerelateerde complicaties tijdens de zwangerschap.

Wat is het verband tussen HVZ en zwangerschap?

Zwangerschap in combinatie met HVZ komt niet toevalligerwijs voor. Tijdens de zwangerschap veranderd het vrouwenlichaam. Wat het hart en de vaten betreft krijgen vrouwen onder andere meer bloedvolume en een lagere vaatweetstand en bloeddruk. Ook wordt de hartslag sneller.[10-14] Daarnaast is het zo dat de bloedstolling toeneemt.[15] Dit heeft logischerwijs invloed op het hart, de vaten, en daarmee op HVZ.

Bij vrouwen die al een HVZ hebben, kan dit alles leiden tot ernstige complicaties tijdens de zwangerschap, zoals hartfalen en zelfs de dood. Voor vrouwen met bepaalde typen HVZ (bijvoorbeeld pulmonale hypertensie) wordt een zwangerschap daarom vaak zelfs afgeraden.[9] Daarnaast ontstaan er soms problemen met de medicatie die vrouwen met een HVZ gebruiken. Bepaalde medicatie kan afwijkingen aan het ongeboren kind veroorzaken. Andere medicatie, zoals bepaalde anti-stollingsmedicatie, werkt minder goed door de lichamelijke veranderingen die plaatsvinden tijdens de zwangerschap.[9] [16] Van sommige medicamenten, zoals de nieuwste antistollingsmiddelen (de directe orale anticoagulantia, DOACs), is de effectiviteit en veiligheid tijdens de zwangerschap zelfs nog niet goed onderzocht, terwijl deze middelen al wel op de markt zijn.[17] [18]

Bij vrouwen die nog niet bekend waren met een HVZ kunnen de genoemde veranderingen tijdens de zwangerschap leiden tot het ontstaan van een HVZ. Zo kan de verhoogde stollingsneiging tijdens de zwangerschap bijvoorbeeld leiden tot een hartinfarct veroorzaak door een bloedstolsel. Herkenning van deze ziektebeelden kan moeilijk zijn, omdat de symptomen lijken op de ongemakken die normaal ook tijdens de zwangerschap voorkomen. Zo kan bijvoorbeeld pijn op de borst tijdens de zwangerschap worden veroorzaakt door zuurbranden, maar ook door een hartinfarct. Daarnaast is het zo dat dokters bij deze jonge vrouwen niet snel aan een HVZ zullen denken, omdat dit relatief zo zeldzaam is in deze leeftijdscategorie.

Niet alleen het herkennen, maar ook het stellen van de diagnose wordt tijdens de zwangerschap bemoeilijkt. Verschillende testen kunnen tijdens de zwangerschap niet gebruikt worden, omdat ze sowieso afwijkend zijn tijdens de zwangerschap (bepaalde bloedtesten), of omdat ze risico geven voor het ongeboren kind (bijvoorbeeld een CT-scan). Zelfs het hartfilmpje is tijdens de zwangerschap anders dan daarbuiten en is daardoor moeilijker te interpreteren. [19] [20] [21]

Het doel van dit proefschrift

Het doel van dit proefschrift is ten eerste het evalueren van specifieke oorzaken van moedersterfte door HVZ in Nederland, en het zoeken naar manieren om moedersterfte in de toekomst te voorkomen. Daarna hebben we dit proefschrift meer toegespitst op bepaalde ernstige HVZ met een hoog risico op moedersterfte. We hebben ons hierin gericht op de diagnose en het risico van de zwangerschap, en de behandeling (onder andere door gebruik van antistollingsmedicatie).

In het kort zochten we naar mogelijkheden en aanbevelingen voor verbetering van de zorg rondom de zwangerschap van vrouwen met HVZ, in een poging een bijdrage te leveren aan een afname van moedersterfte en complicaties veroorzaakt door HVZ.

Wat heeft dit proefschrift bijgedragen

In **hoofdstuk 2** hebben we onderzoek gedaan naar de 96 vrouwen die gedurende 21 jaar in Nederland zijn overleden aan HVZ. De conclusie van dit onderzoek was dat de kans op moedersterfte aan een HVZ in Nederland laag is, met een risico op sterfte van 2.4 vrouwen per 100.000 levend geboren kinderen. De belangrijkste doodsoorzaken zijn het scheuren van de aorta (aortadissectie, 21%), een hartinfarct (21%) of een cardiomyopathie (21%). Een groot gedeelte van de sterfgevallen bleef echter onverklaard (28%). In een klein gedeelte van de gevallen was sterfte mogelijk te voorkomen geweest. Zo werd een aantal vrouwen zwanger tegen medisch advies in, of herkenden dokters de ziekte niet op tijd. Dit laatste onderstreept nog eens het nut van dit proefschrift.

In dit hoofdstuk maakten we een aantal aanbevelingen om de zorg voor vrouwen met een HVZ tijdens de zwangerschap te verbeteren. Een eerste aanbeveling is dat vrouwen met een (eerstegraads-) familielid met een cardiomyopathie of acute onbegrepen dood, moeten worden gescreend op een cardiomyopathie voordat ze zwanger worden. Daarnaast zagen we hoe belangrijk het is om pijn op de borst tijdens de zwangerschap serieus te nemen. Dit kan namelijk duiden op een hartinfarct of een aortadissectie; een belangrijke boodschap voor de medische wereld. We zagen dat het risico op een HVZ of een complicatie hiervan, niet voorbij is wanneer de zwangerschap afgerond is. Het risico blijkt gedurende de gehele kraamperiode verhoogd. Daarnaast zagen we dat vrouwen met een hartziekte goed moeten worden begeleid tijdens de zwangerschap, met name vrouwen met een kunst hartklep (hartklepprothese). Deze specifieke groep onderzochten we verder in hoofdstuk 7.

In **hoofdstuk 3-6** hebben we de nadruk gelegd op de derde oorzaak van moedersterfte zoals gevonden in hoofdstuk 1: het hartinfarct (ischemische hartziekten).

In hoofdstuk 3 en 4 hebben we onderzoek verricht naar hartinfarcten die voor het eerst ontstaan tijdens de zwangerschap of in het kraambed. Dit hebben we gedaan door het verrichten van uitgebreid systematisch literatuur onderzoek (1975-2013) en het beschrijven van casuïstiek uit Nederland. We concludeerden dat een hartinfarct tijdens de zwangerschap, of in het kraambed, begint met pijn op de borst (95%) en met name ontstaat laat in de zwangerschap (3e trimester) of in het kraambed (71%). We vonden dat de belangrijkste oorzaken zowel het scheuren van een bloedvat van het hart (coronair dissectie, 35%, buiten de zwangerschap zeldzaam), als het vormen van stolselpropjes in die bloedvaten zijn (trombus/embolie, 35%). We zagen dat het risico op moedersterfte hoog was (8%), evenals het risico op complicaties bij het ongeboren kind (onder andere 4% sterfte en 56% vroeggeboorte).

In hoofdstuk 5 en 6 hebben we onderzoek gedaan naar vrouwen die al een hartinfarct hadden doorgemaakt en daarna zwanger werden. Dit hebben we gedaan door zowel een groep van 50 vrouwen te onderzoeken, als door systematisch literatuuronderzoek te verrichten waarbij we gegevens uit eerdere onderzoeken hebben opgevraagd (124 zwangerschappen). Hiermee was dit onderzoek het grootste onderzoek in deze groep vrouwen tot nu toe.

We stelden vast dat deze vrouwen een hoog risico liepen tijdens de zwangerschap, met een risico van 1 op 4 op ernstige complicaties, inclusief moedersterfte bij 2%. Slechts 21% van de vrouwen hadden een zwangerschap zonder complicaties betreffende het hart, de zwangerschap en bevalling zelf, of betreffende het kind. We registreerden dat vrouwen met atherosclerose als oorzaak voor hun eerdere hartinfarct het grootste risico liepen.

In **hoofdstuk 7** onderzochten we zwangerschappen van vrouwen met een hartklepprothese. Dat deden we door de 102 zwangerschappen van 52 vrouwen, met een hartklepprothese vanwege aangeboren hartafwijkingen, te evalueren. We concludeerden dat deze vrouwen een hoog risico hebben op complicaties betreffende hart- en vaten, zwangerschap en kraambed en complicaties voor het ongeboren kind (17% had complicaties). Vrouwen met een mechanische hartklepprothese hadden meer complicaties dan vrouwen met een biologische hartklepprothese, maar dit was met name gerelateerd aan de complicaties gerelateerd aan de antistollingsmedicatie die deze vrouwen moesten gebruiken. We zijn daarom in dit onderzoek dieper ingegaan op deze antistollingsmedicatie. Naast het feit dat dit onderzoek een belangrijke bijdrage heeft geleverd aan de kennis rondom het antistollingsbeleid bij zwangere vrouwen, concludeerden we ook dat deze vrouwen en hun medicatie nauwgezet in de gaten en zo nodig aangepast moet worden tijdens de zwangerschap.

In **hoofdstuk 8** onderzochten we het gebruik en de veiligheid van nieuwe antistollingsmedicijnen, de DOACs, tijdens de zwangerschap. Dit deden we door middel van een systematisch literatuuronderzoek van 236 vrouwen die DOACs gebruiken tijdens de zwangerschap. We concluderen hier dat de veiligheid (met betrekking tot afwijkingen bij het kind) en effectiviteit van DOACs tijdens de zwangerschap, niet ondersteund wordt door de huidige literatuur. Het gebruik hiervan tijdens de zwangerschap dient daarom vooralsnog afgeraden te worden.

In het laatste hoofdstuk, **hoofdstuk 9,** onderzochten we de HVZ pulmonale hypertensie tijdens de zwangerschap door middel van een systematisch literatuuronderzoek, gericht op de nieuwe behandelingen voor deze ziekte tijdens de zwangerschap. We zagen dat deze ziekte nog steeds een hoge kans geeft op moedersterfte (16%), ondanks verbetering van de prognose en nieuwe behandelopties. Daarom adviseren we om vrouwen met pulmonale hypertensie nog steeds te stimuleren om niet zwanger te worden.

Hoe nu verder

Hoewel dit proefschrift een significante bijdrage heeft geleverd aan de huidige medische wetenschap, is het slechts een begin. We hebben uitgezocht aan welke HVZ de moeders in Nederland overlijden en hoe we daar mogelijk verbetering in kunnen brengen. Verder zijn we dieper ingegaan op enkele belangrijke ernstige HVZ (hartinfarcten, het hebben van een hartklepprothese vanwege een aangeboren hartafwijking en pulmonale hypertensie) en een belangrijke behandelingsmodaliteit voor veel HVZ: de antistollingsmedicatie. We hebben gezien dat zwangerschap de ontwikkeling van HVZ kan beïnvloeden, met name bij het ontstaan van hartinfarcten. Omgekeerd zagen we dat HVZ complicaties kunnen geven en de uitkomsten van zwangerschap kunnen beïnvloeden.

Terwijl in hoofdstuk 2-6 bekend wordt dat het scheuren van een bloedvat van het hart bij een groot deel van de vrouwen de oorzaak is voor een hartinfarct tijdens de zwangerschap of in de kraamperiode, weten we in de medische wereld nog steeds niet goed hoe dit het beste behandeld kan worden.[24 27] Toekomstig onderzoek zou zich hier op moeten focussen.

In dit proefschrift hebben we gesproken over antistollingsmedicatie van vrouwen met een hartklepprothese. Tevens hebben we de nieuwe antistollingsmedicijnen besproken. Hoewel dit proefschrift veel heeft toegevoegd aan huidige kennis omtrent dit onderwerp, is meer onderzoek, met tevens nadruk op de juiste doseringen tijdens de zwangerschap, nodig. [9 16 28 29-31]

De kennis die we door dit proefschrift vergaard hebben, dient verspreid te worden onder artsen en verloskundigen. Zowel binnen de (geneeskundige) opleiding als daarbuiten (bijvoorbeeld tijdens nascholing en door publicaties in medische tijdschriften). Dat alle hoofdstukken in dit proefschrift zijn gepubliceerd, of aangeboden voor publicatie, is slechts een begin. Er is momenteel veel interesse in de genderspecifieke geneeskunde en de invloed van het vrouwelijke geslacht op ziekten (HVZ) en medicijnen. Waar er weinig gender-specifieker is dan zwangerschap, hoop ik dat deze ontwikkelingen bijdragen aan de verspreiding van de kennis rondom zwangerschap en HVZ. Momenteel is er in mijn eigen specialistische vakgebied, de spoedeisende geneeskunde, gelukkig steeds meer oog voor de invloed van zwangerschap op ernstige medische aandoeningen inclusief HVZ.[22-24] De huidige literatuur legt echter de nadruk op het vóórkomen van en de behandeling van HVZ tijdens de zwangerschap, terwijl mijns inziens er eerst oog dient te zijn voor de herkenning. Want binnen de spoedeisende geneeskunde, valt of staat alles met (h)erkenning.[25 26]

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Curriculum Vitae

Heleen Lameijer was born in Delfzijl, on September 17, 1987. After primary school, high school followed, where she passed her exam in 2005 within two chosen profiles. After high school she went to the city of Groningen to study Medicine. During her internships she worked as an ergometrist at Cavari Clinics, a private clinic runned by Dr.René van Dijk focused on the detection of cardiovascular diseases. During the training there, Heleen came into contact with the semi-acute cardiology, which got her interested. Furthermore, she got acquainted with the cardiologist from the Martini hospital, where she subsequently completed her medical training. During her last internships, she ran her own 'semi-acute chest pain' outpatient clinic under supervision of Dr. Jan Posma. In this period she wrote her first scientific article under supervision of Dr. Robbert Steggerda. She completed her scientific internship under supervision of Dr. Els (P.G) Pieper, titled 'ischemic heart disease during pregnancy'. This internship ultimately resulted in the publication of three scientific articles. In 2012, Heleen obtained her master's degree in Medicine and combined a clinical job within the Cardiology department at Martini Hospital, with a doctoral (PhD) trajectory under supervision of Dr. Pieper and Prof. dr. Dirk Jan van Veldhuisen. Her gained experience in emergency cardiology awoke her passion for emergency medicine. In 2014 she started her residency (specialized medical training) in emergency medicine under supervision of Prof. dr. Jan ter Maaten and Dr. Jorrit Harbers, in the University Medical Centre Groningen. She successfully completed this in 2017, under supervision of emergency medicine physicians Drs. Amanda Drost and Drs. Evelien van der Meeberg. During her training as an emergency medicine physician, Heleen published several emergency medicine related articles. These were mainly focused on emergency cardiovascular pathology and resuscitation, electrocardiography, procedural sedation and analgesia and point of care ultrasound. She also continued her PhD trajectory during her medical training. This resulted in multiple scientific publications, poster presentations and oral presentations at various national and international conferences.

Heleen is currently working as an emergency medicine physician at the Medical Center Leeuwarden in the Netherlands. She combines a clinical with a scientific job, as a principal investigator and supervisor of several research projects in emergency medicine.

Curriculum Vitae *- Nederlands*

Heleen Lameijer is geboren in Delfzijl, op 17 september 1987. Na de basisschool volgde het VWO, waar zij in 2005 haar examen haalde binnen twee profielen. Daarna toog ze richting Groningen om Geneeskunde te studeren. Tijdens haar co-schappen werkte ze als ergometrist bij Cavari Clinics, een privé kliniek van Dr. René van Dijk gericht op de opsporing van cardiovasculaire ziekten. Gedurende de interne opleiding daar, kwam Heleen in aanraking met de semi-acute cardiologie. Haar interesse was gewekt. Hier vond ook haar eerste kennismaking plaats met de maatschap Cardiologie van het Martini ziekenhuis, waar ze vervolgens haar semi-arts stage afrondde. Tijdens deze stage en tijdens haar stage wetenschap draaide ze, onder supervisie van Dr. Jan Posma, haar eigen 'Semi-acute pijn op de borst poli'. In deze periode verscheen haar eerste wetenschappelijke artikel, samen geschreven met Dr. Robbert Steggerda. Haar stage wetenschap volgde Heleen bij Dr. Els (P.G) Pieper, met als onderwerp 'ischemische hartziekten tijdens de zwangerschap'. Deze stage resulteerde uiteindelijk in de publicatie van drie wetenschappelijke artikelen. In 2012 behaalde Heleen haar artsenbul (Master) en combineerde zij een klinische baan bij de afdeling Cardiologie in het Martini Ziekenhuis, met een promotietraject bij Dr. Pieper en Prof. Dirk Jan van Veldhuisen. Mede door de opgedane ervaringen binnen de spoedeisende cardiologie, ontwaakte haar passie voor de acute geneeskunde. In 2014 begon zij, onder begeleiding van toenmalig opleiders Prof. Jan ter Maaten en Dr. Jorrit Harbers, in het Universitair Medisch Centrum Groningen aan de opleiding tot SEH-arts. Deze opleiding sloot ze in 2017 met goed gevolg af, onder begeleiding van huidig opleidend SEH-artsen Drs. Amanda Drost en Drs. Evelien van der Meeberg. Tijdens haar opleiding tot SEH-arts publiceerde Heleen meerdere SEH gerelateerde artikelen. Deze zijn voornamelijk gericht op spoedeisende cardiovasculaire pathologie en resuscitatie, elektrocardiografie, procedurele sedatie en analgesie en point of care echografie. Tijdens de opleiding tot SEH arts continueerde zij bovendien haar promotietraject. Dit resulteerde in meerdere wetenschappelijke publicaties, posterpresentaties en orale presentaties op multipele nationale en internationale congressen.

Momenteel werkt Heleen als SEH-arts KNMG binnen de vakgroep SEH-artsen in het Medisch Centrum Leeuwarden. Zij combineert een klinische met een wetenschappelijke baan, als hoofdonderzoeker en supervisor van meerdere onderzoekstrajecten binnen de spoedeisende geneeskunde.

Dankwoord

Het aangaan van dit promotietraject en het schrijven van dit proefschrift is achteraf gezien voor mij het begin geweest van het verleggen van intellectuele en persoonlijke grenzen in een zoektocht naar het vinden van autonomie, vrijheid, authenticiteit in professionaliteit, kwetsbaarheid en kracht. In de afgelopen jaren dat ik hier mee bezig ben geweest heb ik veel mensen mogen ontmoeten die mij hebben geïnspireerd, gesterkt en gesteund. Er zijn echter een aantal mensen die een speciale dank verdienen: voor jullie is dit dankwoord.

Mijn grote dank gaat uit naar mijn promotoren. Dr. Pieper, lieve Els, je geloofde in mij als wetenschapper toen ik dat zelf nog niet volledig deed, had geduld, steunde me om mijn hart te volgen richting de spoedeisende geneeskunde en hebt me bovenal geleerd dat ik, ook in de wetenschap en als professional, mezelf kan zijn. We hebben samen onze successen gevierd, met dit proefschrift als kersje op de slagroom op de taart. Daarnaast bleek je ook een persoonlijke coach tijdens belangrijke veranderingen in mijn leven. Ik ben je hier erg dankbaar voor.

Prof. Van Veldhuisen, beste Dirk Jan, bedankt dat je (ik tutoyeer!) hebt geloofd in mij, en mijn ogenschijnlijke brutale insteek hebt weten te doorzien als gedrevenheid en wilskracht. Ik ben ontzettend dankbaar voor de coaching, het vertrouwen, de mogelijkheden en de steun die ik van je gekregen heb.

De leden van de leescommissie, prof. Erwich en prof. Van Gelder. Bedankt voor jullie interesse in en goedkeuring van dit proefschrift. Prof. Angela Maas, naast lid van de leescommissie ben jij de grote inspirator geweest voor mij keuze voor de wetenschap. Jij hebt me aan Els gekoppeld, wat de start is geweest van mijn wetenschappelijke carrière, en bent voor mij een feministisch voorbeeld.

De co-auteurs van de artikelen en hoofdstukken uit dit proefschrift. Joke Schutte, je stelde gastvrij je prachtige huis ter beschikking voor de dataverzameling van hoofdstuk 2 en gaf me daar een heus kantoor met uitzicht. Dit, gecombineerd met het samen drinken van zelfgemaakte cappuccino's, maakte onze onderzoeksamenwerking voor mij tot een waar uitje. Luke Burchill en Candice Silversides, met wie ik een prettige internationale samenwerking heb mogen genieten met hoofdstuk 5 en 6 als resultaat. Marlies Kampman en Ymkje van Slooten, jullie stonden aan de basis stonden van de dataverzameling van respectievelijk hoofdstuk 3 en hoofdstuk 7 uit dit proefschrift, en hebben me wegwijs gemaakt in mijn eerste jaar als onderzoeker. Jan Aalberts, met wie ik hoofdstuk 8 schreef, en Anne Siegmund. Jullie maakten voor mij het CPP congres in Bologna niet alleen tot een groot succes maar tot een ware culinaire

en culturele vakantie. Lucia Baris, bedankt voor je hulp bij hoofdstuk 5 en je persoonlijke support via social media.

De patiënten die vrijwillig hebben deelgenomen aan de PROSTAVA en ZAHARA studies, jullie hulp is ontzettend waardevol in de verbetering voor de zorg van (zwangere) vrouwen met een hart- en vaatziekte. Jullie hulp maakt ons, en mij, betere dokters, waarvoor ontzettend veel dank en waardering.

René van Dijk, de andere van Dijkjes, Maaike en Maartje. De opleiding tot ergometrist en de baan bij Cavari Clinics, waar ik ontzettend heb veel heb genoten, gelachen en geleerd, lagen aan de basis van mijn verdere carrière.

De cardiologen van het Martini ziekenhuis. Ik had me geen gezelligere en veiligere eerste werkplek als semi-arts en net afgestudeerd arts kunnen wensen. Jan Posma, jij gaf me het vertrouwen om veilig kennis te maken met de semi-acute geneeskunde door middel van mijn eigen pijn op de borst poli. Robbert Steggerda, dankzij jouw geduld en supervisie schreef ik tijdens mijn semi-arts stage mijn eerste wetenschappelijke artikel, wat duidelijk smaakte naar meer.

Kinge, jij inspireerde me om SEH-arts te worden. Jan ter Maaten, jij zag in mij de potentie als SEH-arts en nam me aan voor de opleiding. Hiernaast bood je me de ruimte om onderzoek te blijven doen, wat voor mij erg belangrijk is geweest.

De SEH-artsen uit het UMCG, mijn leraren. Martine, Wendel, Bas, Mirjam, Bashar, Edwin, Madeleine en Christian. Amanda en Evelien, jullie dienen als opleiders voor mij als krachtig vrouwelijk voorbeeld. Bedankt dat jullie mij op maat in mijn professionaliteit hebben gecoacht, met oog voor (behoud van) mijn persoonlijkheid. Nasim, jouw vertrouwen en hoge verwachtingen met de juiste zetjes in de rug is een boost geweest voor mijn professionele groei. Je tomeloze ambitie is inspirerend.

Mijn opleidingsgenoten, voorbeelden en sparringpartners. Susanne, Josien en Rosa, Marieke, Sophie, Pieter en Katharina. Bedankt voor jullie steun, de gesprekken, de knuffels, de gore grapjes, het accepteren van mijn overdaad aan selfies in de gezamenlijke whats-app groep en het mogen blijven gebruiken van de AIOS kamer na mijn AIOS tijd. Het spijt me dat ik mijn troep nog steeds niet heb opgeruimd, ik denk dat ik jullie gewoon nog niet los kon laten.

Mijn opleidingsgenoten uit de andere centra, het Isala en het MCL. Britt en Mauri, jullie zijn inspirerende doorzetters. Annemieke en Ytje, jullie eigenheid in het vak is bewonderingswaardig.

Mijn vakgroep, de SEH-artsen van het MCL. Majoline, na de opleiding samen te hebben doorlopen zijn we nu opnieuw collega's, iets waar ik ontzettend blij mee ben. Je bent mijn voorbeeld in je communicatie en professionaliteit, en ik ben je ontzettend dankbaar voor de momenten waarin ik me veilig mocht onderdompelen in jouw warme gezin wanneer ik dat nodig had. Ewoud, jouw kritische blik en hulp bij het wetenschappelijke deel van mijn rol in de vakgroep maakt me beter. Ik ben erg blij dat je me tegenwoordig complimenteert met mijn haar. Djoeke, Maureen, Amber, Anniek, Willemijn, Froukje, Rieneke, Constant, Joris T, Joris D en Emile. Ik ben jullie ontzettend dankbaar voor jullie (financiële) steun met betrekking tot dit proefschrift en volledige vertrouwen in mijn kunnen en ambities. Het is ontzettend bijzonder om terecht te mogen komen in een vakgroep die zowel inspireert in ambitie als thuis voelt als een familie. Ik kan bij jullie, zowel als arts als persoon, volledig mijzelf zijn.

De (mijn!) A(N)IOS SEH van het MCL; Marion, Ellen, Nienke, Pauline, Marieke, Svenja, Ben, Sija en Thea. Jullie leren mij mijn nieuwe rol, die van supervisor, en dagen me hier in uit. Bedankt dat jullie mijn leven makkelijker maken door mij frequent naar het werk te rijden terwijl ik jullie snoepjes op eet.

Mijn lieve paranimfen, Renate en Aniek. Renate, waar we ooit zijn begonnen als concurrenten ben je nu al jaren mijn trouwe bondgenoot en vriendin. We doorliepen samen de opleiding tot SEH-arts en maken nu samen deel uit van de vakgroep SEH in het MCL, waar we de wetenschapspost bekleden. Jij inspireert en motiveert me, maakt me beter. Ik ben ontzettend trots op jou en dankbaar dat je deze dag met mij wilt beleven. Aniek, er is niemand die zo hard juicht voor mij als jij. Je vriendschap en je vertrouwen in mij maken me een betere arts, een beter mens, en een betere vriend. Van iedereen die ik ken leef jij het levendigst. Bedankt voor je uniekheid (aniekheid), je gekte, je ambitie, je humor en je steun.

Mijn familie, de Lameijers en de van Heemskerkjes, met Marlou en Joyce in het bijzonder. Jullie moeten vaak accepteren dat ik gelegenheden mis vanwege mijn professie maar blijven desalniettemin geïnteresseerd en steunend. Robbert, je vond dat je een apart plekje hier verdiende in dit dankwoord (typisch). Bedankt dat ik je geen taart meer hoef te betalen om een kilometer met je te mogen zwemmen.

Marieke, mijn buurvrouw. Naast je professionele hulp bij het schrijven van de populaire samenvatting en het CV, ben jij altijd bereid om liefdevol voor Teddy te zorgen wanneer ik voor werk, opleiding of de wetenschap van huis ben. Dat is voor mij goud waard.

De meiden van de ABC club. Jullie zijn een enorme steun geweest tijdens de co-schappen en daarna, zowel professioneel als persoonlijk. Mariska, jij betrok me bij en schreef samen met mij hoofdstuk 4 van dit proefschrift. Ivonne en Ninke,

dat ik een rol mocht vervullen in jullie bruiloft vond ik ontzettend bijzonder om mee te maken. Helaas zien we elkaar door onze hectische en veranderende levens niet zo vaak als ik zou willen, maar ik hecht grote waarde aan onze vriendschap.

De Nachtvlinders, mijn fladdermeisjes. Ondanks dat we elkaar niet frequent zien voelt het samen zijn met jullie als thuis komen. Gelukkig komen jullie momenteel vanuit alle windstreken terug naar Groningen gevlogen, zodat ik ook letterlijk thuis kan blijven, wel zo makkelijk. Martine, jij weet mij altijd te vertellen wie ik ben wanneer ik dat zelf even niet meer weet. Het onderdeel uit maken van jouw bruiloft was voor mij een kroontje op onze vriendschap.

Mijn vriendinnen; Masha, Sabine, Sanne, Marina, Irina, Jill, Sandra, Naomi en Nathalie. Ik ben ontzettend dankbaar jullie in mijn leven te hebben. Jullie lessen, vriendschap, eerlijkheid, veiligheid en eigenheid is van onschatbare waarde voor mij. Janke en Deborah, onze reis naar Nepal door de Himalaya zat dankzij jullie vol inzichten bijdragend aan mijn persoonlijke en professionele groei, ik hoop dat ons pact stand houdt. Leon, de frequentie waarmee jij mij keihard uitlacht houdt me met beide benen op de grond en maakt vrijwel alles behapbaar. Kim, bedankt voor je oordeelloosheid en je humor. Jouw vriendschap, kookkunsten en zorgzaamheid maken mijn ambities een stuk makkelijker te verwezenlijken. Bernard en Astrid, bedankt voor de gastvrije warmte in december.

Bart en Jelmer, jullie veiligheid, liefde en vertrouwen in mij gedurende belangrijke jaren in mijn leven hebben mij een van mijn belangrijkste eigenschappen helpen te ontwikkelen; lef. Hiervoor ben ik jullie eeuwig dankbaar. Bas, als er zoiets bestaat als een soulmate dan moet jij het wel zijn. Bedankt voor je steun, je liefde en alle levenslessen.

Mijn Oma, in wie ik mij zo herken. Ondanks je hoge leeftijd (93) leef je mijn leven bewust met me mee, en altijd up-to-date (email, iPad, laptop, etc.). Dat je nu om de hoek woont is een enorm geschenk, waar we beiden erg van genieten. Ik hou van jou.

Mijn lieve ouders, Henk en Jenneke. Het is ontzettend belangrijk voor mij geweest om me intellectueel te kunnen ontwikkelen op alle vlakken die ik wilde en jullie hebben er alles aan gedaan om dit voor mij mogelijk te maken. Nooit heb ik hoeven twijfelen of iets wat ik wilde doen of leren wel mogelijk zou zijn, want jullie maakten dit mogelijk. Mamma, als werkende moeder was jij voor mij een voorbeeld van een onafhankelijke vrouw. Dit heeft in grote mate mijn levensvisie bepaald, zonder jou was ik nooit zo zelfstandig geweest. Pappa, jij hebt mij leren doorzetten. Als sporter motiveerde jij mij altijd om het beste uit mezelf te halen, zonder die motivatie was dit proefschrift er nooit geweest. Ik ben jullie hier ontzettend dankbaar voor, en hou van jullie.

Jan Jakob, mijn lieve, slimme, knappe en dappere broertje. Jij begrijpt mij, jij kent mij. Ik ben dankbaar dat onze band ondanks onze fysieke afstand (op dit moment zelfs een halve wereld) zo sterk blijft. Want van alle mensen op de wereld houd ik onvoorwaardelijk het meest van jou.

En natuurlijk Teddy. Altijd Teddy.

Liefs, Heleen.