Pregnancy in Women with Congenital Heart Disease

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To my loved ones

ABSTRACT

Background: The survival for children born with congenital heart disease (CHD) has increased and the majority reach adult age. Having a cardiac problem raise questions on the probability of successful pregnancies and predictors associated with unfavorable outcome. Heart biomarkers are used in emergency care to evaluate patients with chest symptoms. However, normal levels during pregnancy have not been established.

Aims: The aims of the thesis were to study risk of cardiac, obstetric and neonatal outcome of pregnancy in women with CHD, and evaluate two risk-classifications. To obtain additional diagnostic tools when evaluating pregnant women with chest symptoms.

Methods: The participants in Paper I and II were single CHD-center cohorts of 232 and 307 women respectively, with 496 and 580 pregnancies respectively. The women were classified according to two prevalent risk classifications (CARPREG and mWHO). In Paper I we evaluated maternal age and the applicability of risk classifications on cardiac, obstetric and neonatal outcomes of pregnancy. Paper II addressed parity as a covariate for cardiac events. In Paper III national registries, National Patient Register, Medical Birth Register and Cause of Death register were used. Women with CHD born 1953-1997 with first singleton birth 1973-2015 were compared with matched controls without a diagnosis of CHD. Outcomes were cardiac, obstetric and neonatal complications. In Paper IV 196 pre-pregnancy healthy women were recruited from antenatal maternal outpatient clinics. Blood samples were analyzed for heart biomarkers N-terminal pro Brain Natriuretic Peptide (NTproBNP) and high sensitive cardiac Troponin T (hs-cTNT) on four occasions during and after pregnancy.

Results: In Paper I in 496 CHD pregnancies, there were 14% cardiac complications, 14% obstetric and 15% neonatal complications, comparable with previous single- and multicenter publications. Severe complications were rare. Age above 35 years was not associated with worse outcome. The two risk classifications had moderate diagnostic accuracy of 0.71 and 0.65 respectively. In Paper II we analyzed the effect of parity in 307 CHD women. We found a high odds ratio of 5.5 (95% CI, 1.8-16.9) to have the same cardiac outcome of a second pregnancy as the first, if the risk classification remained the same. In Paper III both cardiac, obstetric and neonatal adverse events were more common in 6´131 CHD women than in 158´343 controls, but with low absolute numbers. Severe complications were very rare. Maternal all-cause mortality during pregnancy and one year postpartum was 3/10´000. Perinatal death was 55/10´000 to be compared with 38/10´000 in controls. During the observation time-period the number and complexity of CHD diagnoses increased, as did age at first birth and maternal weight. In Paper IV we established the 95th percentile levels of NTproBNP and hs-cTNT for pre-pregnancy healthy women to be below the cut-off levels for the suspicion of heart failure and myocardial ischemia. Existing cut-off levels can be used also in pregnant women in the emergency room.

Conclusion: Two established risk classifications had moderate diagnostic accuracy. The maternal outcome of a second pregnancy can be expected to be the same as of the first, if in stable cardiac situation. The absolute risks for adverse outcome of pregnancy in women with CHD are low, but higher than in controls. Existing cut-off levels of heart biomarkers can be used also during pregnancy, in pre-pregnancy healthy women.

Keywords: congenital heart disease, pregnancy, risk classification, parity, heart biomarker.

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LIST OF PAPERS

This thesis is based on the following papers.

I Eva Furenäs, Peter Eriksson, Ulla-Britt Wennerholm, Mikael Dellborg. Effect of maternal age and cardiac disease severity on outcome of pregnancy in women with congenital heart disease.
International Journal of Cardiology 243 (2017) 197-203

II Eva Furenäs, Peter Eriksson, Ulla-Britt Wennerholm, Mikael Dellborg. Cardiac Complications during Pregnancy Related to Parity in Women with Congenital Heart Disease.
Cardiology 2020;145:533-541

III Eva Furenäs, Peter Eriksson, Ulla-Britt Wennerholm, Georgios Lappas, Annika Rosengren, Mikael Dellborg. Pregnancy in women with congenital heart disease; a nationwide population based register study
In manuscript

IV Eva Furenäs, Peter Eriksson, Ulla-Britt Wennerholm, Mikael Dellborg. Pregnancy in healthy population: dynamics of NTproBNP and hs-cTroponin T.
Open Heart 2020;7:e001293. doi:10.1136/openhrt-2020-001293

SAMMANFATTNING PÅ SVENSKA

Graviditet hos kvinnor med medfött hjärtfel

Bakgrund:
Barn som föds med hjärtfel överlever i betydligt högre utsträckning numera till vuxen ålder. Unga kvinnor med medfött hjärtfel (CHD, congenital heart disease) som funderar över graviditet har många frågor om eventuella komplikationer, både för egen del och för ett framtida barns del. Två hjärtmarkörer (NTproBNP och hs-cTNT) används vid akut andnöd eller bröstsmärta för att utesluta hjärtsvikt eller hjärtmuskelskada, men normalvärden för hjärtfriska gravida kvinnor har inte funnits.

Syfte:
Att studera hjärtrelaterade (kardiella), graviditetsrelaterade (obstetriska) och fosterrelaterade (neonatala) utfall i samband med graviditet hos kvinnor med CHD, samt utvärdera två risk-klassifikationer. Att förbättra rådgivning till unga kvinnor med medfött hjärtfel inför en eventuell graviditet. Att fastslå normalvärden hos hjärtfriska gravida kvinnor för hjärtmarkörer.

Metod:
I delarbete I och II studerade vi hur det går vid graviditet hos kvinnor med medfött hjärtfel som följs på GUCH/ACHD-centrum, Göteborg. Vi analyserade andel kardiella, obstetriska och neonatala komplikationer utifrån ålder och paritet (antal graviditeter). Vi utvärderade också två tidigare föreslagna risk-klassifikationer. I delarbete III använde vi Socialstyrelsens nationella register med avidentifierade löpnummer och samkörde Patientregistret, Medicinska födelseregistret (MFR) och Dödsorsaksregistret. Utfall var kardiella, obstetriska och neonatala komplikationer hos förstföderskor med singelgraviditet som fanns i MFR 1973-2015, där vi jämförde kvinnor med medfött hjärtfel med en kontrollpopulation från samma tidsperiod. Delarbete IV var en analys av hjärtmarkörer (NTproBNP och hs-cTNT) hos hjärtfriska gravida kvinnor. Blodprov för hjärtmarkörerna togs vid två tillfällen under graviditet, efter förlossning samt 6 mån efter graviditeten.

Resultat:
Vi analyserade utfallet av 496 CHD-graviditeter och fann 14% kardiella, 14% obstetriska och 15% neonatala komplikationer vilket är jämförbart med andra center (delarbete I). Det var få allvarliga komplikationer. Ålder över 35 år ökade inte risken för komplikationer. De två risk-klassifikationerna var användbara till en måttlig grad. I delarbete II fann vi hög sannolikhet (odds ratio 5.5 (95% CI, 1.8-16.9) för att en andra graviditet skulle ha samma risk för hjärtkomplikation som den första, under förutsättning att CHD-kvinnans hjärtsituation var oförändrad. I registren i delarbete III fanns 6´131 förstföderskor med CHD-diagnos som jämfördes med 158´343 kontroller utan CHD-diagnos. Kardiella, obstetriska och neonatala komplikationer var vanligare hos CHD-kvinnor jämfört med kontroller, men i absoluta tal var det låga risker och allvarliga komplikationer var mycket ovanliga. Mödradödlighet (av alla orsaker) under

graviditet och ett års uppföljning var 3/10´000 hos CHD-kvinnor. Barnadödligheten (t o m 6 dagar efter födseln) var 55/10´000 hos CHD att jämföra med 38/10´000 hos kontroller. Antalet CHD-kvinnor och svårighetsgraden av CHD ökade under tidsperioden, så också förstföderskornas ålder och vikt. I delarbete IV beskrev vi normala nivåer för hjärtmarkörerna hos kvinnor under och efter graviditet. Dessa nivåer var under de gränsvärden man använder i övriga befolkningen vid misstänkt hjärtsvikt och hjärtmuskelskada och man kan därför använda samma gränsvärden hos gravida kvinnor som hos övriga befolkningen.

Slutsats:
De två risk-klassifikationerna har ett begränsat värde. Det är sannolikt att en andra graviditet är förenad med samma risk för hjärtkomplikation som vid den första, om mammans hjärtsituation är oförändrad. Det är låg risk för allvarliga komplikationer i samband med graviditet hos kvinnor med CHD, men högre jämfört med kontroller. De gränsvärden som finns för hjärtmarkörer (NTproBNP och hs-cTNT) är användbara även hos gravida, tidigare hjärtfriska, kvinnor.

CONTENTS

ABBREVIATIONS AND EPONYMS

ACHD	Adult congenital heart disease
APGAR	Appearance, pulse, grimace, activity, respiration
ART	Assisted reproductive technology
ASD	Atrial septal defect
AUC	Area under the curve
BMI	Body Mass Index
CHD	Congenital heart disease
CI	Confidence interval
CS	Cesarean section
eGFR	Estimated glomerular filtration rate
ESC	European society of cardiology
EVF	Erythrocyte volume fraction
GUCH	Grown up congenital heart disease
gw	Gestational weeks
Hs-cTNT	High-sensitive cardiac TroponinT
ICD	International classification of diseases
IQR	Inter-quartile range
IVF	In-vitro fertilization
LBW	Low birth weight
MBR	Medical birth register
NPR	National patient register
NTproBNP	N-Terminal pro Brain Natriuretic Peptide
PFO	Patent foramen ovale
PPH	Postpartum hemorrhage
PTB	Preterm birth
ROC	Receiver operating characteristic
SD	Standard deviation
SGA	Small for gestational age
SHBG	Sexual hormone binding globulin
TPR	Total population register
WHO	World Health Organisation

Eisenmenger syndrome	Cyanotic heart defect caused by shunt.
Fontan circulation	Operation technique where the caval veins are connected to the pulmonary artery.
Tetralogy of Fallot	Congenital heart defect; pulmonary stenosis, hypertrophic right ventricle, VSD and overriding aorta.
Mustard-operation	Operation technique for transposition of the great arteries, where the blood is redirected via atrial reconstruction.

INTRODUCTION

Historical and to-date perspective

Historical perspective on congenital heart disease

The modern era of congenital heart disease (CHD) surgery started in the 1940´s with the Blalock-Taussig shunt to enhance blood supply to the pulmonary circulation[1]. In 1944 the first operation of a child with coarctation of the aorta was performed by Professor Crafoord in Sweden[2]. Since then the number of pediatric cardiac operations have increased to approximately 900 per year in Sweden divided between two centers; Gothenburg and Lund[3].

Advances in diagnostics of congenital heart disease, pediatric cardiac surgery and anesthesiology, catheter interventions and general health care have resulted in an increase of adult patients with CHD who survive into adulthood at a good health[4-7]. Nowadays the number of persons with CHD is higher among adults than among children due to high survival rates[4]. We experience the expected concomitant increase in pregnancies among women with CHD[8-10]. To separate the adult patients with CHD from the pediatric population the term Adult Congenital Heart Disease (ACHD) has been in use in American literature, while Grown Up Congenital Heart Disease (GUCH) was used in European literature until recently. Since this is a new category of patients to adult cardiac care, as well as obstetric care, research is ongoing to evaluate different perspectives on the outcome for both mother and child.

Approximately 1% of the population is born with CHD[4, 11-14]. The fetal heart starts evolving early and at 6-7 weeks of age the heart is beating and four heart chambers are developed[15]. Many of the cardiac defects develop during this time, including conotrunchal defects and the structural changes may progress during pregnancy. Abnormal valves affect blood flow and may lead to restricted development of heart chambers or pulmonary circulation[16, 17]. Birth rates of children with CHD may change with increasing fetal diagnostics[11]. Between 1999 and 2011, the termination rate of pregnancies in Sweden for all detected CHD was 2% while between 2012 and 2016 it increased to 2.9%. For the severe heart defects, (for example hypoplastic left heart syndrome) the termination rate increased from 33% to 52% during the same time period. One year survival rate for neonates with severe CHD increased during the same period from 82% to 86%[14].

To-date congenital heart disease

CHD is a heterogeneous group of more than four hundred different diagnoses and more than thousand combinations. Figure 1 shows the distribution of diagnoses in the Swedish register of congenital heart disease, SWEDCON[3]. The most common heart defects are septal defects (yellow), which cause shunts between the atrias or between the ventricles. The four heart valves can be atretic or stenotic which might affect the development of the ventricles. There may be a re-arrangement of atrias, ventricles, arterial or venous vessels. Sometimes several defects are combined. The

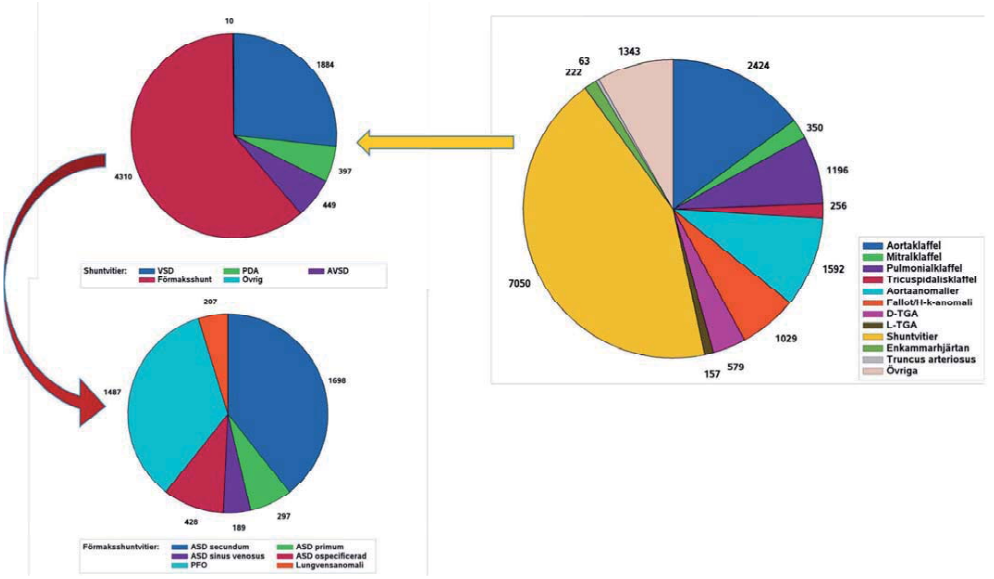


Figure 1. Distribution of CHD diagoses in the SWEDCON register. Published with courtesy of SWEDCON.

diversity in lesions imply a diversity in survival rate, type of complications, interventions and comorbidities. Some patients are operated at a young age, with different operation techniques and outcome, while some CHD diagnoses with less symptoms are diagnosed at an adult age. There is a slight predominance of male neonates in the incidence of the total CHD cohort, but for some diagnoses (i.e. atrial septal defect) there is a female predominance. Survival rates for CHD have increased the last decades and we are still in the beginning of understanding about the impact of acquired cardiovascular disease on patients with congenital heart disease[18]. There is also an increasing interest in the association between obstetric events, e.g. preeclampsia, and the risk of future acquired cardiovascular disease in the normal population[19]. Since survival has increased for women with CHD the long-term effects of obstetric complications, the impact of pregnancy on future CHD prognosis and morbidity will be important to study.

Specialized outpatient clinics for patients with CHD started in the late 1990´s, entitled GUCH or ACHD clinics since the existing adult cardiology care units merely cared for acquired coronary disease or heart failure in the older population. The GUCH/ACHD center in Gothenburg, Sweden was initiated in 1996 and is one of two tertiary centers in Sweden with cardiac interventions and specialized thoracic surgeons. We have close collaboration with the obstetric ward with regular multidisciplinary conferences on the management of pregnancy and delivery since 2008. CHD-cardiologists, anesthesiologists and dedicated obstetricians take part in the conferences, together with midwives, arrhythmia specialists and other concerned disciplines. The primary catchment area is Gothenburg with surroundings (approximately 1.5 million inhabit-

ants) and we have referrals from Western and Northern Sweden (altogether approximately 4.5 millions).

Historical and to-date obstetric care in Sweden

Sweden, together with Norway and the Netherlands had already in the beginning of the 20th century low maternal mortality compared to other countries and it continued to decline during the century. In 1904 the maternal mortality rate in Sweden was 230/100´000 births which in 2015 had declined to 4/100´000[20-22]. The reason is probably multifactorial, but advances in medical, obstetric and antiseptic care and the education of community spread midwives may be partial explanations. Perinatal death rates have been stable around 3.7/1´000 live births for the last decade, while it was 7/1´000 in 1973[23]. Approximately 100´000 children are born every year in Sweden. The Swedish Medical Birth Register (MBR), hosted by the Swedish National Board of Health and Welfare ("Socialstyrelsen") started in 1973 and continuously receive information from antenatal clinics, delivery wards and pediatric examination of the newborn. From these reports, we have data on, for example, the rate of cesarean section (CS) of 5.3% in 1973 that increased to 17.3% in 2018[24-25]. In Western countries the maternal age at first birth has increased and comorbidities are more common in primiparous (first birth) women compared to some decades ago[10, 26-27]. In Sweden, age at first birth has increased from 24.6 years in 1978 to 28.8 years in 2018. Body Mass Index (BMI) at first antenatal visit has increased from 23.0 in 1992 to 24.7 in 2018 and the proportion of obese women with BMI ≥30 has increased during the same time from 6% to 15.4%. On the other hand, smoking at first antenatal visit has decreased from 31.4% in 1983 to 4.2% in 2018[25]. The first child following assisted reproductive technology (ART) in Sweden was born in 1982 and the number of births has increased over time. ART includes standard in vitro fertilization, intracytoplasmic sperm injection, freezing and thawing of embryos and oocyte and sperm donation. Today approximately 5´000 children per year are born after reproductive therapy[25, 28].

Physiology and biomarkers

Normal pregnancy physiology

The first signs of cardiovascular changes of pregnancy start early after conception. Trophoblasts invade the spiral arteries and affect the endothelium and smooth muscle layers to become a high-flow low-resistance system in the placenta[29].There are changes in the uterine artery with increased flow and lower pulsatility index within a few weeks after conception[30-32]. The peripheral resistance in the vessels is reduced allowing an increase in blood flow. There is an increased water resorption from the kidneys resulting in plasma volume expansion and hemodilution and an increased glomerular filtration[33]. There are several humoral changes involved causing these changes of the cardiovascular system with adaptive endothelial and vascular function and reduced aortic stiffness[34, 35].The changes in the peripheral circulation demand an increased cardiac output which is obtained by an increase in both heart rate and stroke volume[34, 36-38]. The figure below show that the hemodynamic changes are increasing until gestational week (gw) 20-25 when there is a plateau until term when the vascular resistance becomes somewhat increased[36, 39, 40]. There are few hemodynamic

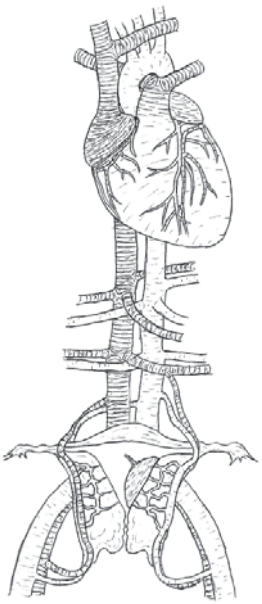


Figure 2. Drawing of heart and uterus. Non-pregnant vessels in the uterus to the left, and during pregnancy with placenta to the right. Published with permission from Sixten Furenäs.

studies during labor and the early postpartum phase. During delivery cardiac output is increased with the uterine contractions, presumably when blood is auto-transfused from the uterus[38]. Cardiac output remains raised for at least 48 hours after delivery despite a fall in heart rate, due to an increase in venous return from the utero-placental circulation[41]. Within a month postpartum, cardiac output has returned to normal[42].

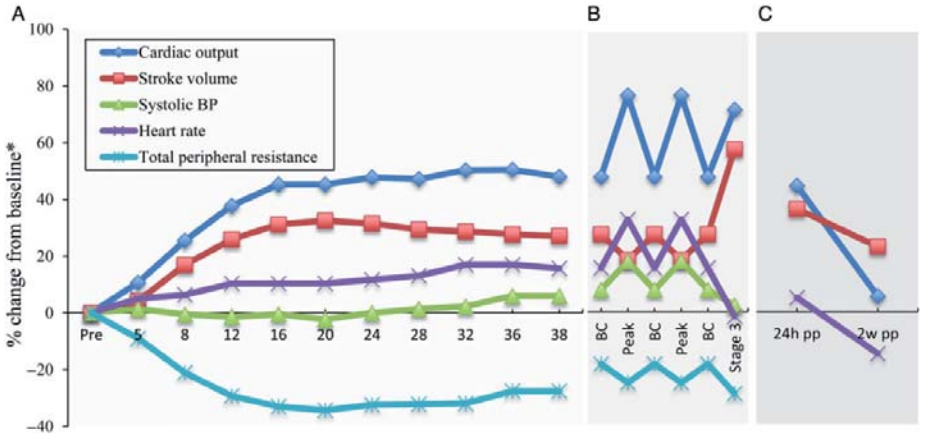


Figure 3. Hemodynamic changes with respect to gestational weeks (A), during labor (B) and 2 weeks postpartum (C)[40]. BP blood pressure, pp postpartum, BC between contractions. *For cohorts in (B) and (C), relative changes from baseline were compared with the baseline values of the cohort from (A). Published with permission from Oxford University Press.

Echocardiographic findings in normal pregnancy

The cardiac performance is dependent on preload, afterload, heart rate and contractility. Left ventricular mass, dimension and left atrial size increase during pregnancy, but contractility seem to remain unchanged in several publications. Changes in volumes and ventricular mass return to normal within one year postpartum. Some studies also found reduced diastolic function at the end of pregnancy, which was reversed within one year. Right heart volume is also significantly increased both in pregnancy and at one-year follow up compared to non-pregnant women[37, 42-44].

Biochemical changes in normal pregnancy

There are several changes in biochemical test results during pregnancy due to the circulatory changes, the increased metabolic demands and hemostatic, humoral and immunologic response. The increase in water resorption lower the erythrocyte volume fraction (EVF) or hematocrit, and subsequently hemoglobin (Hb). When renal glomerular filtration rate increase by 60% during pregnancy it affects the turn-over of biomarkers, why the reference levels at the analyzing lab might be misleading[45].

The use of heart biomarkers

Several heart biomarkers reflecting ventricular wall stress or cardiac myocyte injury have been studied in previous publications on heart failure or ischemic heart disease populations[46, 47]. The guideline recommendations of cut-off levels to rule out heart failure (NTproBNP <300 ng/l) and myocardial infarction (hs-cTNT <14 ng/l) are accepted among clinicians[48, 49]. In heart failure literature, both Brain Natriuretic Peptide (BNP) and N-Terminal Brain Natriuretic Peptide (NTproBNP) have been studied[48]. In Sweden, NTproBNP with longer half-time is more often used than BNP[50-52]. Normal levels in blood donors are reported and serve in some studies as reference population. The levels of NTproBNP were higher with age and higher for females compared to males within the same age groups in a study on 1980 blood donors. Females in age group 18-29 years had median level of 37 pg/ml and in age group 60-69 the median was 68 pg/ml. Corresponding median levels for males were 20 and 43 respectively[53]. In the same study, the effect of renal function on NTproBNP levels was studied and median level was 38 pg/ml in blood donors with GFR >91 ml/min and 46 pg/ml in persons with GFR 60-90 ml/min. The association with impaired renal function has been confirmed in primary care studies and heart failure studies[54-56].

The association between NTproBNP and sex has been studied with focus on hormones. In a Framingham study population, higher NTproBNP was associated with female sex, with the highest levels in premenopausal women receiving oral contraceptives. In both sexes, higher NT-proBNP levels were corresponding to lower free testosterone and higher sexual hormone binding globulin (SHBG), adjusted for age, BMI and cardiovascular risk factors[57]. In postmenopausal women higher NTproBNP levels were associated with lower androgens and higher SHBG[58, 59]. High BMI was associated with low natriuretic peptides in a Framingham population[60]. The same pattern was seen in the ICON study on NTproBNP and BMI[61]. There also seem to be differences in levels in different ethnicities with lower levels in Afroamericans and Chinese persons compared to Europeans[62]. Diseases that can cause ventricu-

lar wall stress except for systolic heart failure, for example hypertension or thyroid disease, exhibit elevated levels of NTproBNP[63, 64]. Hyperthyroid patients had more than doubled levels of NTproBNP compared with euthyroid controls without significant changes in left ventricular dimensions or systolic function[65]. In CHD literature NTproBNP levels vary with complexity of congenital heart disease[65]. The European guidelines on ACHD recommend serial testing of NTproBNP to identify patients at risk of cardiovascular events. Levels above 15.2 pmol/l (or 136 ng/l) has been shown to have prognostic value on cardiovascular events and mortality after adjustment for age, sex, type of congenital diagnosis and ventricular function[66, 67]. In a study on cyanotic patients, the effect of high hematocrit (or EVF) was discussed as a contributing factor to the 12-fold higher NTproBNP in cyanotic patients compared with controls[68]. In the same study oxytocin seemed to stimulate release of NTproBNP in atrial myocytes.

In modern ischemic heart disease literature troponins (Troponin I, Troponin T, high sensitivity cardiac Troponin T (hs-cTNT)) have been studied[47, 49, 69]. At Sahlgrenska University Hospital, Gothenburg analyzing lab, hs-cTNT is used, mostly in the emergency room setting to rule in or rule out myocardial infarction. Troponins are thought to be released in the blood as a result of myocyte necrosis due to ischemia or inflammation. Advanced age and impaired renal function are associated with increased levels of troponins, while female sex is associated with lower levels[70-72]. Other conditions (respiratory disease, sepsis among others) may also exhibit elevated troponins[73]. Several studies have shown increased troponin levels with exercise; spinning, marathon and cycling competition. However, there are diverging opinions if the increase during exercise is a result of cardiac cell destruction or from release of troponins from the cytosolic compartment of myocytes[74]. In a CHD cohort, hs-cTNT was higher in diagnoses that are more complex, in arrhythmia, and systemic systolic dysfunction[75].

Heart biomarkers during pregnancy

There are some publications on different biomarkers in healthy pregnant women with blood samples taken at selected time-points during pregnancy, labor and/or postpartum[42, 76-79]. In a study on 94 pregnant women NTproBNP was highest in the end of the first, and beginning of the second trimester (median 73 ng/l at 11-15 gw) compared with the third trimester (median 41 ng/l in 33-41 gw) and a different cohort of non-pregnant women (38 ng/l)[76]. In another publication on 51 pregnant women NTproBNP was elevated during the first trimester (median 43 ng/l) compared with second and third trimester (28 ng/l). Measurements 2-6 days postpartum were the highest (median 127 ng/l) and were higher in women delivered with cesarean section (not indicated whether acute or elective) than vaginal delivery[42]. Similar findings of postpartum levels were found in a study on 116 women with median levels of 46 ng/l in the second trimester, 36 ng/l in the third trimester and 108 ng/l within 2 days postpartum. At six months postpartum in the same cohort, levels were 41 ng/l[77]. Sample size and study design, timing of blood samples and choice of controls were different in the studies why direct comparison is difficult. A related natriuretic peptide, BNP, has been evaluated in pregnancy studies, but is not used at our lab[80-83]. Pregnancy related complications of preeclampsia or peripartum cardiomyopathy have shown to be associated with increased levels of NTproBNP[84]. Women with severe preeclampsia

had ten times higher median levels of NTproBNP compared with women with gestational hypertension or normal subjects[85]. There was a strong positive correlation between NTproBNP and creatinine. In pregnant CHD women, NTproBNP above 128 ng/l at 20 gw predicted cardiovascular events during pregnancy[86].

Cardiac troponins, but not hs-cTNT, have been studied in few publications during pregnancy. In a study on 51 healthy women during labor and early peripartum levels of several cardiac markers were studied. They found Troponin I (TNI) to have the highest level 24 hours postpartum but still below upper limit of normal for that assay (0.134 vs 0.15 ng/mL)[79]. When obtaining repeated hs-TNI during pregnancy in 51 healthy women third trimester levels were higher than first trimester (median 1.3 vs 0.8). The highest levels were found day 2-6 postpartum (median 2.3 ng/l) and higher in women with vaginal delivery compared with cesarean section. There was no information on upper limit of normal[42]. In a study on 150 women divided in non-pregnant, healthy pregnant and hypertensive pregnant women cTNT was not elevated in healthy pregnant women at 36 weeks gestation compared to non-pregnant but significantly increased in preeclamptic women[78].

Pregnancy-associated complications in general population

Table 1. Pregnancy complications in general population

Obstetric complications	**Frequency**
Miscarriage	15-20/100 (early in pregnancy)
Hypertensive disorders of pregnancy	2-8/100
Thromboembolism	13/10´000
Postpartum hemorrhage	3-7/100
Gestational diabetes	1-14/100
Peripartum cardiomyopathy	1/5´700
Maternal mortality	12/100´000
Neonatal complications	
Preterm birth	5/100
Low birth weight/small gestational age	5-6/100
Perinatal death	4-5/1´000

Frequencies refer to populations in high income countries, further described in text.

Obstetric complications in general population

Miscarriage and terminations

Miscarriage occur frequently, even though not always recognized if it occurs early in pregnancy. At 4-6 weeks gestational age, the rate of pregnancy loss is 15%-20%. The most common cause is chromosomal abnormalities within the fetus. Other causes can be infections, thrombophilia, uterine abnormalities or endocrine disorders[87]. In a Swedish study, 25% of ever-pregnant women reported at least one miscarriage[88].

Prenatal screening has increased the termination rate of fetuses with chromosomal defects the last twenty years. The proportion of terminations for severe congenital heart defects discovered prenatally has also increased from around 8% to 11% during the same time. There are different termination rates for different cardiac diagnoses with just over 50% termination rate for hypoplastic left heart syndrome[14]. The information given to the parents, gestational age, future prognosis, social situation, local law among other factors influence the decision[89].

Hypertensive disorders of pregnancy

Pregnancy can be complicated by pregnancy-induced hypertension (gestational hypertension) or preeclampsia. Both are defined as systolic blood pressure ≥140 and/or diastolic ≥90 mmHg on more than one occasion, after 20 weeks of gestation. In preeclampsia there is also end-organ involvement with renal proteinuria (≥300 mg/24 h), renal insufficiency, thrombocytopenia, impaired liver function, neurological symptoms or fetal growth restriction as manifestations[90-92]. Seldom preeclampsia progress into eclampsia with seizures, which is a life-threatening condition. Preeclampsia complicates 2-8% of pregnancies in different populations, with 4.8% in a Nordic population with a higher incidence (5-10%) in the first pregnancy[93, 94]. Risk factors for preeclampsia is previous preeclampsia, multiple gestation, diabetes mellitus, chronic hypertension, obesity, age above 35 years and ART among others[91, 94, 95]. The underlying cause is not fully understood but seem to involve angiogenic imbalances in the maternal-fetal circulation. There is an association between preeclampsia and future maternal cardiovascular disease[96]. Hypertensive disorders account for 10-25% of maternal deaths worldwide; in Sweden it is the most common direct (i.e. no underlying disease) cause of maternal death, accounting for 15% of all maternal mortality in Sweden 2007-2017[93, 97]. Fetal complications associated with hypertensive disorders are preterm birth, intrauterine growth restriction and perinatal mortality.

Thromboembolism

There is an increase in coagulation factors II, VII, VIII and X during pregnancy that promote thrombosis. Together with stagnation of venous return caused by the growing uterus, there is an increased risk of pulmonary embolism, pelvic thrombosis and deep venous thrombosis during pregnancy[98-100]. A Swedish register study found an incidence of venous thromboembolism of 13/10 000 pregnancies. Half of them were within the first twelve weeks postpartum. There was an association with cesarean section, smoking and preeclampsia[101]. Thrombophilia, previous thromboembolism, obesity, advanced age, caesarean section and immobilization, multiple gestations are some risk factors reported in other publications[102]. Pulmonary embolism is one of the most common direct cause of maternal mortality in high resource countries and the second most common direct cause in Sweden, accounting for 10% of all maternal deaths[97, 103].

Postpartum hemorrhage

Postpartum hemorrhage (PPH) is a common cause worldwide to maternal mortality but in high resource countries, the mortality rate is low among the 3-7% of all pregnancies complicated with PPH. There are different definitions used for PPH; one of them is >500 ml blood loss at vaginal delivery or >1000 ml at cesarean section (which

is difficult to assess). After cesarean section, the blood is mixed with amniotic fluid why a higher volume is accepted. Another definition is 10% lowering of hematocrit or erythrocyte volume fraction (EVF, the fraction of red blood cells in the blood volume), which will be influenced by the plasma volume[104, 105]. In Sweden PPH is defined as >1000 ml irrespective of delivery mode. The main cause is to be found within the obstetric situation with retained placenta, uterine atony, lacerations or instrumental delivery associated factors. Risk factors are among others previous PPH, coagulopathies, multiple gestation, obesity, and of course anticoagulation medication.

Other maternal complications

Gestational diabetes mellitus complicates 1-14% of pregnancies, depending on the studied population, definition and screening methods. Risk factors are among others obesity, familial diabetes, advanced maternal age and previous gestational diabetes. Since the risk factors tend to remain the recurrence rate in the next pregnancy is high[106, 107]. Other endocrine complications as suboptimal thyroid function may occur[108].

Cardiac complications during pregnancy are not common in the general population. Peripartum cardiomyopathy, when heart failure develops at late pregnancy or within the first months postpartum without previously known heart disease, is associated with preeclampsia. Since the incidence is varying in the world, genetic factors might play a role[109]. In Sweden, the incidence was one per 5 719 deliveries in 1997-2010[110]. Spontaneous dissection of coronary vessels is an unusual cause of myocardial infarction in the population, but do occur in pregnant women[111]. Aortic dissection in women without genetic syndromes is unusual, but was the most common indirect cause of death in a Swedish national cause-of-death register study[20]. Atherosclerotic ischemic heart disease has increased coinciding with increased maternal age and BMI. Ischemic heart disease is associated with increased maternal mortality[103, 112]. In a systematic review 32% of women with pre-existing ischemic heart disease had cardiovascular complications during pregnancy and congenital anomalies in the offspring was found at a higher rate than expected[113].

Maternal mortality

The incidence of maternal mortality, up to one year postpartum, is varying between different pats of the world with 216 maternal deaths per 100´000 live births in 2015, or 0.2%, which is a 44% decrease since 1990 according to WHO reports[21, 114]. Direct causes of maternal mortality are defined as complications associated with the pregnancy, while indirect causes are associated with concomitant disease. Hemorrhage is the leading cause of maternal death in Africa and Asia, while hypertensive disease caused the majority of the maternal deaths in Latin America. In high income countries, the maternal mortality was 12 per 100´000 live births in 2015, corresponding to a lifetime risk of maternal mortality of 1 in 4900 in high income countries compared to 1 in 36 in sub-Saharan Africa. In the Nordic countries maternal mortality in the general population was 7.2/100 000 live births 2005-2013[115]. In UK/Irish, Nordic and Swedish reports cardiovascular disease is the main indirect cause of maternal mortality[97, 103, 115]. Figure 4 shows cause of maternal deaths (n=168) in the Nordic countries 2005-2013. The major cause of cardiovascular deaths in the Nordic countries was

aortic dissection (10 out of 28). In the latest UK/Irish report 2009-2014 the majority of cardiac deaths were sudden arrhythmic deaths (47 out of 153) and ischemic heart disease (34 out of 153). CHD accounted for 3 out of 28 of cardiac deaths in the Nordic report and 11 out of 153 in the UK/Irish report. The majority of cardiac deaths occurred 1-42 days postpartum.

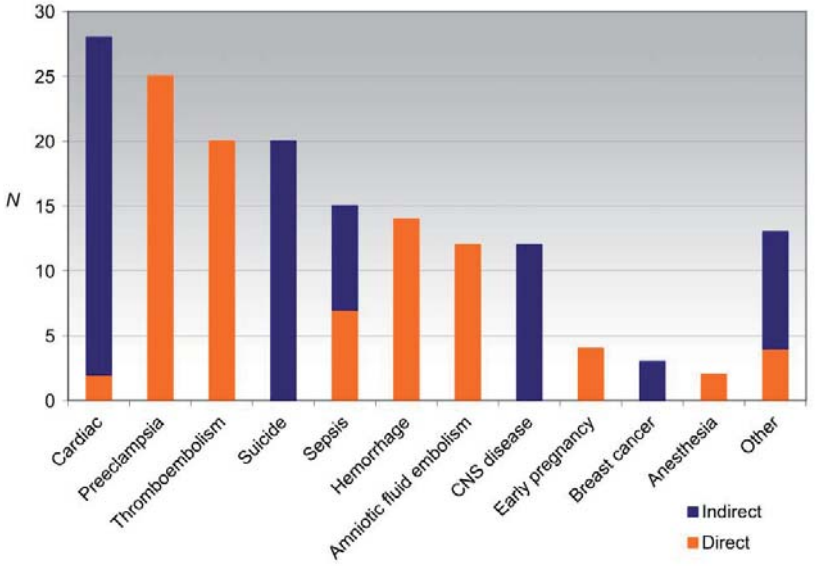


Figure 4. Cause of maternal deaths (n=168) in the Nordic countries 2005-2013[115]. Published with permission from John Wiley and Sons.

Delivery mode

Delivery mode is affected by tradition and cultural aspects as well as the health care services provided in different countries. In a WHO world enquiry in 2012 54 countries had cesarean section (CS) rates of <10%, and 46 countries have figures of >20%. In Sweden the CS rate was 17%, in Canada 26%, in the USA 30% and in the Netherlands 13%[116]. Negative consequences of CS are intraoperative injury, hemorrhage, infection and thromboembolism as well as complications associated with an upcoming pregnancy. In a comparison between vaginal delivery and CS without medical indication the OR for hemorrhage was 2.5 (95% CI, 2.1-3.0) and for infection 2.6 (95% CI, 1.8-3.8) for women delivered with CS. There were also increased risks for the infants, for instance respiratory problems[117]. Statistics from Swedish National Board of Health and Welfare report around 17% CS in Sweden from 2006 to 2018. In recent years the proportion of planned CS has increased compared with acute CS (9.6% vs 7.6%)[25].

Fetal/neonatal complications in general population

Preterm birth

Preterm birth (PTB) is defined as delivery before 37 gw (or <259 days) from the first day of the woman's last menstruation. Very preterm birth is defined as delivery before 32 gestational weeks[118]. There are two main categories of PTB: medically indicated PTB or spontaneous PTB. Medically indicated are PTB caused by maternal or fetal complications (decision by obstetrician, sometimes called iatrogenic PTB). Spontaneous PTB can start with either spontaneous preterm pre-labor rupture of the membranes or spontaneous preterm labor with intact membranes. Spontaneous PTB comprises 60-75% of all PTBs and 25% to 40% are indicated[119, 120]. Risk factors for spontaneous PTB are previous preterm birth, maternal disease, and pregnancy characteristics (e.g. multiple birth, infections or smoking)[121, 122]. In Sweden the rate of PTB before 37 gw was 5.4% in 2018[25]. In a population-based study 1991-2001 on preterm births, 55.2% were spontaneous and 20.2% were indicated (75% vs 25% when excluding intrauterine fetal death, congenital malformations and unknown onset). The authors found an association with PTB and smoking, primiparity, and advanced maternal age[119]. PTB account for 75% of perinatal mortality and have a risk of long-term morbidity with neurodevelopmental, gastrointestinal or respiratory problems[120, 123].

Low Birth Weight/Small for Gestational Age

Low Birth Weight (LBW) is defined as birth weight ≤2500g and very low birth weight is defined as birth weight ≤1500g. There are several definitions on Small for Gestational Age (SGA) based on estimation of gestational age, birthweight and sex and is a statistical measurement. One definition is a birthweight more than two standard deviations below the gestational age and sex specific reference curve[124, 125]. Intrauterine growth restriction is another term in literature, which means that the rate of fetal growth is less than normal for the growth potential of that specific infant. There are several risk factors for LBW and SGA; sociodemographic, maternal pre-existing disease, obstetric complications (e.g. hypertensive disorders of pregnancy) and multiple pregnancy. The incidence of low birth weight varies in the world and is 5-6% in the Scandinavian countries[126, 127]. Complications for the fetus include risk of perinatal mortality, intellectual/behavioral difficulties, cerebral palsy and metabolic syndrome at adult age[128, 129].

Stillbirth/Perinatal death

The definition of stillbirth is fetal death ≥22+0 gestational weeks (before July 2008 it was ≥28+0 gestational weeks in Sweden)[130]. Perinatal death include stillbirth and early neonatal death <7 days. The rates of perinatal death differ worldwide depending on socioeconomic factors and health care systems. In the year 2000 Sweden had less than 5/1000 total births while parts of Africa and Asia had 70-100 perinatal deaths/1000 total births in a WHO report[131]. In low and middle income countries infections, poor maternal care and hypertensive disease are some causes. In high income countries perinatal mortality is associated with preterm birth, maternal medical issues including hypertensive disease and smoking[132]. Late neonatal death (day 7-27) was 30/1000 live births in the world in the year 2000 and in western Europe 3/1000 live

births[131]. The rate of stillbirths in Sweden was 3.7/1000 live births and early neonatal death 1.5/1000 in 2015[23].

Pregnancy-associated complications in women with heart disease (congenital and acquired)

Cardiac complications during pregnancy in women with heart disease (congenital and acquired)

In the literature on pregnancy and heart disease, the cohorts often consist of both congenital and acquired heart disease. Acquired heart disease include for example rheumatic valvular disease, ischemic coronary disease and arrhythmia without structural abnormalities. When possible, the CHD proportion of the cohorts were identified in the studies and specified below.

Heart failure

Heart failure, when there is insufficient cardiac output to support oxygenation of the tissues, is reported to occur in 1.6% to 13.1% of pregnancies in women with heart disease[133, 134]. Heart failure is defined in different reports as either symptoms significant for heart failure, hospitalization, echocardiographic/radiologic findings and/or an International Classification of Diseases (ICD) code of heart failure. In women with pre-existing heart disease, onset of peripartum cardiomyopathy on top of the heart disease is most likely not possible to distinguish from heart failure caused by the underlying heart disease. Heart failure is more common in the third trimester and early postpartum than in the first and second trimester[135]. In studies on maternal congenital heart disease exclusively, the rate of heart failure is 1.6-6.2%[133, 136]. Cardiac diagnosis and morphology, previous cardiac events and comorbidities, socioeconomic factors and health care system contribute to outcome.

Arrhythmia

Arrhythmias are common in pregnancy, even without pre-existing cardiac disease, as a consequence of increased plasma volume and hormonal changes[137]. Supraventricular tachycardia of short duration is not uncommon in normal population pregnancies[138]. Some of the CHD diagnoses have an increased risk of arrhythmias also without pregnancy, due to hemodynamic factors or surgical scarring. Arrhythmias in the context of heart disease in pregnancy literature is defined as either electrophysiological registration of tachycardia, hospitalization, initiation of medication against tachycardia or clinically strong suspicion of hemodynamically important arrhythmia.

The incidence of arrhythmia during pregnancy in women with heart disease is reported to be from 0.6% in a low risk population to 9.1% in a Brazilian cohort with a majority having acquired heart disease[133, 139-141]. Previous episodes of arrhythmia is naturally a strong predictor for arrhythmia during pregnancy. Arrhythmias seem to be more common in the second and third trimester than early in pregnancy or postpartum[135, 142, 143]. Women with heart disease, especially valvular disease, and atrial fibrillation or flutter during pregnancy have a higher mortality compared to women without atrial arrhythmia, probably reflecting a more severe heart condition[143, 144]. In the CHD subgroup of a multinational prospective study arrhythmias were prevalent in

2% of the pregnancies to be compared with 0.2-0.7% in two American general population obstetric discharge note registers[136, 143-145]. A multicenter retrospective study on CHD women exclusively reported 4.7% arrhythmias during pregnancy[133].

Thromboembolism

Pregnancy is associated with an increased risk of thromboembolism. In CHD, the cyanotic heart defects, such as Eisenmenger syndrome, have an impaired hemostasis with increased risk of both thrombosis and hemorrhage[146]. Patients with shunts without cyanosis (e.g. simple secundum atrial septum defect, ASD) are not known to have an increased risk of thromboembolism per se in the absence of predisposing factors as thrombophilia (hereditary, factor V Leiden). On the other hand, if the ASD patient is affected by venous thrombosis there is a possibility for paradoxal embolization from venous to arterial vessels causing coronary embolus, stroke or other end-organ ischemia[147, 148]. In the general population, the prevalence of patent foramen ovale (PFO) is estimated to 15-25%[149, 150]. The presence of PFO allow for paradoxal embolization but has no hemodynamic impact and is not considered a congenital heart defect, however the ICD-code is the same as for ASD. Thromboembolism during pregnancy in women with heart disease is not reported in all publications. When data are available, an incidence of 0.6 to 2.8% is reported[141, 151]. In the CHD subgroup in a large multicenter register, thromboembolism was reported in 1.5% of pregnancies[136]. Thromboembolism during pregnancy in women with mechanical valve prosthesis is a feared complication, why anticoagulation regime need to be addressed[86, 103, 133, 152].

Mortality

Mortality during pregnancy or in the peripartum period in women with heart disease has been reported to be 0.4% to 1% in large cohorts of women with various structural heart diseases in a multicenter register[140, 153]. In the subgroup of CHD pregnancies maternal mortality was reported to 0.2%[136]. Depending on study cohort mortality has been reported to be as high as 3.6% in a Brazilian study[141]. However, mortality was not specified as cardiac cause in those publications. In a Canadian publication, cardiac death was reported in a cohort consisting of 64% women with CHD to be 0.3% during pregnancy and six months of follow up[135]. In selected subgroups such as Eisenmenger syndrome the mortality rate is reported to be as high as 8 to 36%[154, 155].

Structural changes

There are some studies with echocardiographic evaluation during and after pregnancy in CHD patients[156-159]. Cornett et al found signs of reduced diastolic function in women with structural heart disease during and 6 months after pregnancy compared with pre-pregnancy measurements[156]. Uebing et al compared CHD-women with and without pregnancy and had similar echocardiographic findings in both cohorts except for women with Tetralogy of Fallot patients. Women with this CHD-diagnosis had persisting increase in right ventricle volume after pregnancy[157]. Guedes et al followed women with Mustard-operated transposition before, during, and more than 2 years postpartum. They found persisting systemic ventricle dilatation and dysfunction, however there was no control population[158]. In pregnant women with the same CHD diagnosis, with non-pregnant women and men as controls Bowater et al found increased deterioration of the systemic ventricle in the pregnant women[159].

There are few long-term reports on the effect of pregnancy on future complications, the need for reoperation or future perspectives. Balint et al found cardiac complications during pregnancy in CHD women to be associated with cardiac events and interventions within a median follow up of 2.6 years[160]. In a questionnaire follow-up 11 years after last pregnancy two thirds of the 65% who answered the questionnaire reported good health, which correlated with physical activity. Ten patients out of 158 died during the follow up (with a substantial proportion of lost to follow up)[161]. There is an increasing interest in pregnancy-related complications, such as preeclampsia, and risk of future cardiovascular disease in normal population[162-164]. The association with CHD pregnancy complications and future acquired cardiovascular disease has not been studied.

Obstetric and neonatal complications in women with heart disease (congenital and acquired)

Miscarriage

The rate of miscarriages is difficult to estimate since the pregnancy may not have been reported to health care providers. In a multicenter study patients with heart disease were enrolled at the first antenatal visit and they reported a miscarriage rate after their first visit of 3%[151]. When using a Dutch/Belgian registry on congenital heart defects exclusively with retrieval of medical records the miscarriage rate before gestational week 20 was 19.4%[133]. In a literature review of 48 retrospective publications on different CHD diagnoses, a total 15% miscarriage rate was reported although varying between diagnoses with Fontan circulation and cyanotic heart defects with the highest incidence of 40%[165]. Oxygen saturation <85% is associated with growth restriction, preterm birth and high incidence of perinatal death[166].

Hypertensive disorder of pregnancy

Preeclampsia/eclampsia occur in 2.2-4.7% in different publications on heart disease to be compared with 2-5% in Western healthy populations[133, 136, 153, 165, 167]. In a Canadian register study, the incidence of severe preeclampsia was 1.9% in the CHD population compared to 1.3% in women without CHD[168]. There may be differences in the incidence of preeclampsia between different lesions. Some studies include ART treated patients while data on other risk factors for preeclampsia not are addressed, such as multiple birth[133, 165, 169]. Coarctatio aortae (CoA) is a CHD-lesion with an increased risk of pre-existing hypertension. In a multicenter study, 2.6% of pregnancies in CoA women were complicated by preeclampsia and the risk was higher if there was pre-existing hypertension[170]. Similar results, which are in accordance with the general population, were found in CoA in a Dutch CHD register cohort[171]. A recent meta-analysis failed to identify CHD as a risk factor for preeclampsia[172].

Postpartum hemorrhage

Postpartum hemorrhage is reported to occur in 2.4–11.5% in cohorts of women with heart disease with the majority being CHD populations[133, 136, 139, 151, 153]. Obstetric health care services, delivery mode and medication may affect the incidence. In women with mechanical valves, which require anticoagulation, the incidence of postpartum hemorrhage is 10%[152]. The use of anticoagulants and cyanotic heart disease have been shown to be associated with postpartum hemorrhage[151].

Delivery mode

Delivery mode varies by tradition and health care services in different countries for the general population as well as for women with heart disease. In a Canadian study of women with heart disease, 27% were delivered by cesarean section (CS) with a majority being for obstetric indication (96%). There was no significant difference in cardiac events in women delivered vaginally (3%) or by CS (4%)[151]. Vaginal delivery occurred in 65% of the patients and CS in 35% (primarily for obstetric indication) in women with heart disease in a report from Brasilia. In <5% of these cases, CS was indicated by heart disease, such as diseases of the aorta, cardiomyopathy, Eisenmenger's syndrome, severe left ventricular obstructive outflow diseases, or pulmonary vascular disease[141]. There is no consensus in mode of delivery with different cardiac diagnoses where one must weigh the negative consequences of CS against the possibility to plan for a complicated delivery with adequate personnel and consultants present. In a multicenter study on women with various heart diseases 44% delivered with CS. An analysis showed no difference in outcome between planned CS and vaginal delivery except for the neonates being more preterm and with lower birth weight in the CS group[173] . In Sweden the rate of CS in the general population has been approximately 17% the last decade[174]. The ESC guidelines state that CS for cardiac reason should be considered for patients presenting in labor on oral anticoagulants, with aggressive aortic pathology, or in acute intractable heart failure. CS is advised in severe forms of pulmonary hypertension including Eisenmenger's syndrome[175].

Assisted reproductive technology

The use of assisted reproductive technology (ART) has increased the last decades. Women with some CHD diagnoses seem to have an increased risk of infertility and increased use of ART compared with healthy women[169]. The use of ART is associated with a higher rate of hypertensive disorders of pregnancy, preterm birth and low birth weight mainly due to the higher rate of multiple pregnancy in ART compared with spontaneous conception. However, also ART singletons have a higher risk for adverse perinatal outcome[176, 177].

Fetal/neonatal outcomes

Preterm birth (12-18%), low birth weight or small for gestational age (3.7-14%) are the most common neonatal adverse outcomes[133, 139, 151]. The cause of preterm birth is multifactorial and a proportion is iatrogenic and indicated by the maternal cardiac, obstetric or fetal condition. Kloster et al found an association between PTB, SGA and complexity of maternal CHD. Educational level was also associated with these neonatal complications, however independent of CHD[178]. There is a higher incidence of fetal (1-1.3%) and neonatal (0.3-1.2%) deaths in women with acquired and congenital heart disease compared to healthy women[139, 151]. Some multicenter studies report a total fetal loss of 1.5-4%[133, 136]. The offspring outcomes are highly correlated to maternal cardiac complications during pregnancy[133]. Women with CHD were more often born preterm themselves and gave birth to preterm neonates in a Swedish register study[179]. The interaction between cardiac performance and utero-placental blood flow has also attracted some interest since the infants of women with CHD more often are delivered PTB and SGA[180-182].

Familial recurrence of cardiac malformation

Recurrence of CHD is probably multifactorial with genetic, socioeconomic and environmental contributing factors. There are different reports on the rate of recurrence of congenital heart defects in the offspring of women with CHD. There are also autosomal inherited syndromes with CHD as common feature, e.g. Noonans syndrome, 22q11-deletion syndrome. Multifactorial recurrence (i.e. no detected gene) were reported to have recurrence rates between 1% to 5.8% in a review, while autosomal dominant are inherited in 50%[183].

Some studies report birth defects as a group, and not specified as congenital heart defects. A Swedish nationwide register study found an increased risk of any birth defects in neonates of CHD women compared to non-CHD (6.7% vs 3.6%)[179]. When analyzing the recurrence in neonates to men with CHD during the same era in Sweden they found no difference between men with or without CHD[184]. The data were on all birth defects as one group and were registered only at birth. A Canadian register study found major visible congenital anomalies in 1.3% vs 0.6% in women with CHD compared to non-matched controls[168]. The registration of anomalies in these studies is reported from birth discharge notes and some defects may not have been found within the perinatal period.

A Danish report with linking of several nationwide registries including a multi-generation register found a relative risk of 3.21 (95% CI, 2.96-3.49) for CHD in first-degree relatives. Depending on type of lesion the recurrence risk was three- to eightyfold compared to total population with a CHD prevalence of 103 per 10 000 live births. Of the CHD-cases in the population 2.2% were attributed to CHD in a first-degree relative[185]. Children with CHD are more often born with intrauterine growth restriction according to a recent review[186]. The European guidelines on congenital heart disease report recurrence rates depending on diagnosis of 2% to 18% for women and 1% to 4.5% for men[67].

CHD cohort studies and risk classifications

CHD cohort studies

There is an increasing amount of literature on women with cardiac disease and pregnancy, Table 2. Most of them are retrospective cohort studies and there are a few prospective register studies and national registry studies. There are no randomized trials on, for example, delivery mode or medication due to ethical and medical reasons. Some publications focus on women with CHD, while others also include women with acquired heart disease. In most studies, outcomes are cardiac, obstetric and neonatal events, but some focus on maternal cardiac events.

Considering the hemodynamic changes in normal pregnancy the concern has been whether women with low cardiac output from start can increase cardiac output corresponding to the demands from the fetus and if the increase in plasma volume would cause congestion. Women with outflow valvular stenoses can only increase stroke

volume to a certain degree and thereby have a restricted cardiac output even if the ventricles are unaffected. Pre-existing arrhythmias can accelerate during pregnancy and cause hemodynamic instability. The growing uterus cause venous congestion and decreased preload which can cause symptoms in preload dependent circulations such as Fontan circulation.

Table 2. Listed below are a summary of some of the large clinical cohort studies (>100 pregnancies) and their outcomes

Cohort	Era	Type	n of women	n of pregnancies	% ACHD	Outcome % of total cohort
Siu et al 2001 (151) (CARPREG I)	1994-1997	Multicenter, prospective	546	599	74	Mortality 0.8 Cardiac 13 Obstetric 9 Neonatal 20
Avila et al 2003 (141)	1989-1999	Single center, retrospective	[a]	1000	19	Mortality 2.7 Cardiac 23 Obstetric n.a. Neonatal 12[e]
Drenthen et al 2010 (133) (ZAHARA)	1980-2007	Multicenter register, retrospective	714	1302	100	Mortality not reported Cardiac 8 Obstetric 29[d] Neonatal 30
Roos-Hesselink et al 2013 (153) (ROPAC Preg 1)	2007-2011	Multicenter register, prospective	[a]	1321	62	Mortality 1 Cardiac 15 Obstetric 9 Neonatal 17[e]
Roos-Hesselink et al 2019 (136) (ROPAC Preg 2)	2007-2017	Multicenter register, prospective	[a]	5739 [b]	57	Mortality 0.6 Cardiac 16 Obstetric 8 Neonatal 29
Silversides et al (135) (CARPREG II)	1994-2014	Multicenter (two), prospective	[a]	1983[c]	64	Mortality 0.3[f] Cardiac 17 Obstetric n.a. Neonatal n.a.

Cardiac complication include heart failure, arrhythmia, and thromboembolic event. Mortality include all cause mortality. Obstetric complications include pregnancy-induced hypertension, (pre)eclampsia, and postpartum hemorrhage. Neonatal complications include fetal and neonatal mortality, preterm birth, low birth weight. The complications are not mutually exclusive. [a]Number of women not reported. [b]Of whom 1321 were derived from previous study . [c]Of whom 289 (14%) pregnancies were derived from previous study. [d]Include preterm labor and HELLP syndrome. [e]Low birth weight not presented. [f]Only cardiac cause of death reported. N.a. = not applicable.

Table 3. Risk classifications

Classification	Predictors	Cardiac risk	Neonatal risk	Calculation
CARPREG I (151)	Prior cardiac event NYHA functional class > II or cyanosis, Left heart obstruction Systemic ventricular dysfunction. Multiple gestation Smoking Heparin/warfarin	1p 1p 1p 1p	 1p 0.75 p 3 p 1 p 1 p	Cardiac risk: 0 p: 5 % 1 p: 27 % ≥ 2 p: 75 % Neonatal risk: Increasing with points, no specified percentages.
ZAHARA (133)	Prior arrhythmia NYHA functional class III/IV Left heart obstruction (peak LVOT gradient >50 mm Hg or aortic valve area <1.0 cm2 Mechanical valve prosthesis Systemic atrioventricular valve regurgitation (moderate/severe) Pulmonary atrioventricular valve regurgitation (moderate/severe) Cardiac medication before pregnancy 1. Cyanotic heart disease (corrected and uncorrected) Twin or multiple gestation Smoking during pregnancy	1.5 p 0.75 p 2.5 p 4.25 p 0.75 p 0.75 p 1.5 p 1.0 p	 2.5 p 0.75 p 0.75 p 1.75 p 0.5 p	Cardiac risk: <0.50 p: 2.9 % 0.51–1.50 p: 7.5% 1.51–2.50 p: 17.5% 2.51–3.50 p: 43.1% >3.51 p: 70% Neonatal risk: <0.50 p: 19.9% 0.50–0.99 p: 33.3% 1.0–1.49 p: 46.7% ≥1.50 p: 59.6%
CARPREG II (135)	Prior cardiac event or arrhythmia Baseline NYHA III-IV or cyanosis Mechanical valve Ventricular dysfunction High risk left-sided valve disease Pulmonary hypertension Coronary artery disease High risk aortopathy No prior cardiac intervention Late pregnancy assessment	3 3 3 2 2 2 2 2 1 1		Cardiac risk: 0-1 p: 5% 2 p: 10% 3 p: 15% 4 p: 22% >4 p: 41% Neonatal risk: Not evaluated.
mWHO (175, 187)	Small or mild pulmonary stenosis, patent ductus arteriosus, mitral valve prolapse. Successfully repaired simple lesions Atrial or ventricular ectopic beats.	Class I		Class I: no detectable increased risk of maternal mortality and no/mild increase in morbidity. Cardiac risk: 5-10%
	Unoperated atrial or ventricular septal defect Repaired tetralogy of Fallot Most arrhythmias Turner syndrome without aortic dilatation	Class II		Class II: small increased risk of maternal mortality or moderate increase in morbidity Cardiac risk: 5.7-10.5%
	Mild left ventricular impairment Hypertrophic cardiomyopathy Native or tissue valve disease not considered WHO I or IV Mild aortopathy Repaired coarctation Atrioventricular septal defect	Class II-III		Class II-III: intermediate increased risk of maternal mortality or moderate to severe increase in morbidity Cardiac risk: 10-19%
	Moderate left ventricular impairment Previous peripartum cardiomyopathy without any residual impairment Mechanical valve Systemic right ventricle mildly decreased ventricular function Fontan circulation. Unrepaired cyanotic heart disease Other complex heart disease Moderate mitral stenosis Severe asymptomatic aortic stenosis Moderate aortaortopathy Ventricular tachycardia	Class III		Class III: significantly increased risk of maternal mortality or severe morbidity Cardiac risk: 19-27%
	Pulmonary arterial hypertension Severe systemic ventricular dysfunction Previous peripartum cardiomyopathy with residual impairment Severe mitral stenosis Severe symptomatic aortic stenosis Systemic right ventricle with moderate or severely decreased ventricular function Severe aortopathy Vascular Ehlers–Danlos Severe (re)coarctation Fontan with any complication	Class IV		Class IV: extremely high risk of maternal mortality or severe morbidity, pregnancy is contra-indicated Cardiac risk: 40-100%

The Siu et al cohort was a Canadian multicenter study including 13 hospitals. The authors considered the selection bias to be low. In the CHD proportion of the cohort (n=434), 7% had a cardiac event, half of them heart failure and there was one death. From the total cohort predictors for adverse events were found, entitled CARPREG I score, Table 3.

The cohort from Avila et al was a single center Brazilian cohort with the majority of patients having rheumatic valve disease. The complications in the total cohort were high with maternal mortality 2.7% and stillbirth 2.9%. In the CHD proportion of the cohort (n=191 pregnancies) heart failure was reported in 11.5%, arrhythmia in 2%, maternal mortality 3.7%, preterm birth 16% and stillbirth 5.2%. The majority of maternal mortality were in Eisenmenger patients. In the total cohort of heart disease, including rheumatic valve disease, there were 26 pregnancies with mechanical valve prosthesis of whom four had thromboembolic events. No specific predictors were evaluated in the study.

Drenthen et al reported data from the national databases on CHD in the Netherlands and Belgium run by seven tertiary centers. It is a retrospective study of medical charts, excluding deceased patients why mortality was not reported. There was a selection of patients giving informed consent to review the records. Besides the predictors from the CARPREG I score the authors found three additional predictors for adverse cardiac and neonatal events in a multivariate analysis entitled ZAHARA, Table 3.

Both cohorts from Roos-Hesselink et al are from the ROPAC investigation (Registry of Pregnancy and Cardiac Disease), which was initiated by the European Society of Cardiology (ESC) Working Group on Grown-Up Congenital Heart Disease and Valvular Heart Disease 2007. The register include prospective data from 53 high- and low-income countries. There is likely to be a selection bias from centers with more frequent cases of heart disease in pregnancy. Mortality was reported up to one week postpartum. The participants in the two reports were somewhat different with a higher proportion of women from emerging countries and with more severe heart disease in the later report.

Silversides et al reported cardiac events exclusively, from a cohort of women receiving care at two tertiary care centers, Toronto and Vancouver. The authors separated the predictors into general, lesion-specific and delivery-of-care predictors. In addition to previous CARPREG I and ZAHARA predictors, the authors found additional predictors of unfavorable outcome, Table 3.

In addition to predictors derived from cohort studies, a risk classification adapted from World Health Organization based on cardiac lesions was proposed[187]. It was adopted in the ESC guidelines on cardiovascular diseases during pregnancy[175]. Lesions were classified modified WHO class I-IV with I judged as low risk and IV recommended against pregnancy, Table 3.

Evaluation of risk classifications

The risk classifications have been evaluated by external datasets[139, 140, 188-192]. Depending on study design, collection and selection of cohorts, risk profile of cohorts, definition of complications and health care systems, among other factors the performance of the classifications differ[193]. For the CARPREG I the area under the receiver operating characteristic (ROC) curve (AUC) is 0.57-0.73, for the ZAHARA score 0.68-0.74 and mWHO 0.65-0.77. The CARPREG II score was recently evaluated in a pilot study of 100 patients with similar AUC as CARPREG I[194].

Adding pre-pregnancy signs of heart failure or atrial fibrillation and no previous cardiac intervention was suggested to increase the AUC for mWHO score in the ROPAC registry[140]. In a meta-analysis shown below (Figure 5) the risk models were considered to have a moderate discrimination where the mWHO and ZAHARA were found to be somewhat better in predicting cardiac complications in women with congenital heart disease than CARPREG I[195].

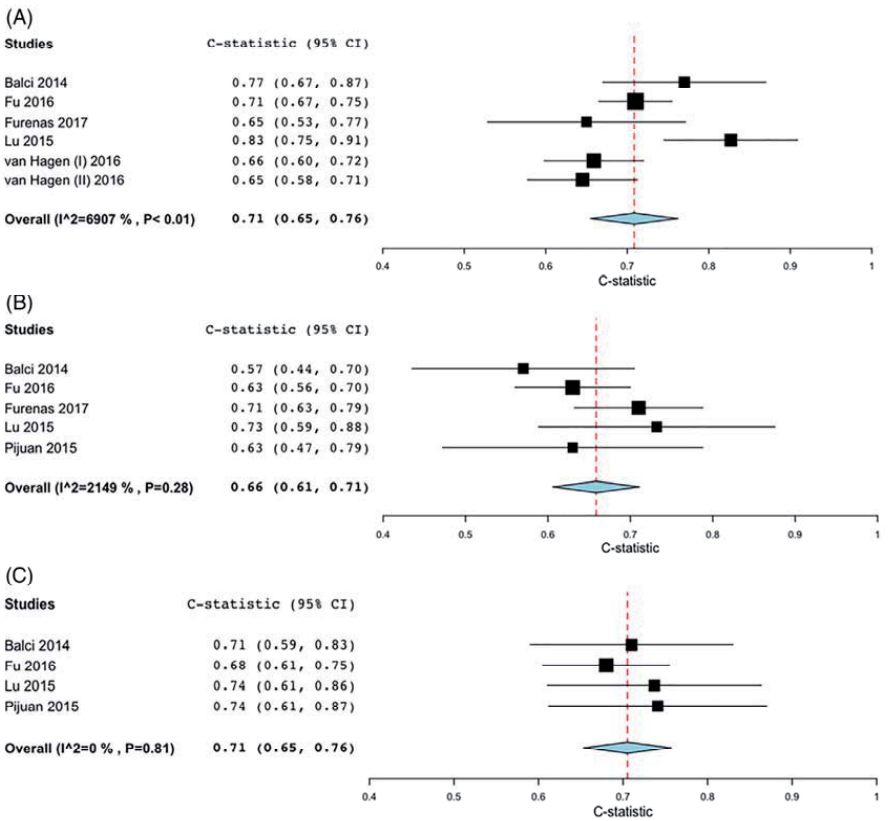


Figure 5. Meta-analysis of risk classifications, Wang et al[195]. Pooled area under the curve c-statistic for the A) modified World Health Organization (mWHO), B) CARPREG I and C) ZAHARA scores. Published with permission from John Wiley and Sons.

The study by Balci et al was a prospective multicenter study with a diversity of CHD diagnoses, while one third of the patients in the retrospective study by Lu et al had surgically corrected shunts[188, 190]. The cardiac complication rate was higher in the Balci study, which indicate a cohort with more severe CHD. The study by Fu et al was on a Chinese CHD cohort consisting of 76% shunt lesions of whom almost half were operated[191]. The Pijuan cohort were 31% non-CHD[189]. The van Hagen cohort was from the ROPAC register[140].

Nationwide register studies on CHD and outcomes of pregnancy

The Danish and Swedish registries are similar with the possibility to link between registries based on a unique personal identification number. In Sweden reporting to registries have been mandatory since 1987 to National In-Patient Register (NPR), to National Out-Patient Register since 2001 and since 1973 to the Medical Birth Registry (MBR). In Denmark, inpatient diagnoses have been reported since 1977 and outpatient diagnoses from 1995 onwards. The Danish Medical Birth Register started in 1978. Discharge note registries, as in the American and Canadian reports, are not linked to personal identification number why the registration report number of hospitalizations and not number of patients. There is a possibility that the same person is registered several times. Further, it is not possible to link between registries and the possibility to do long-term follow up is less. The publication from Hayward et al covers only the state of California. Canada have two registration systems with Quebec separated from the rest of Canada. They report discharge notes with the same disadvantages as for the American register studies. The maternal and neonatal outcomes are reported as composite outcomes in the Canadian study (Table 4).

Table 4. Nationwide register studies on CHD and pregnancy

First author	Country/state	Era	Database characteristics/sample derivation	N of CHD	N of controls	CHD classification	Outcome	Result
Josefsson (12)	Sweden	1986-2006	Women born 1973-1983, alive at 13y. Linkage between national registries: Medical Birth (MBR), Total Population, National Patient, Cause of Death and Multi-generation Registries	2216 women of whom 691 in MBR	492 476 of whom 188´176 in MBR	Simple/ complex (by authors)	Data on woman´s own birth, nativity, first delivery and neonatal outcome	CHD women more often born preterm, SGA, multiple gestation and also delivered preterm, SGA and recurrence
Kloster (13)	Denmark	1997-2014	Women with singleton pregnancies in Medical Birth Registry linked to National Patient Registry	3688 pregnancies	929 084	Simple, moderate, complex	Effect of maternal age on Preterm birth, SGA	Preterm and SGA more common with increased age but no difference CHD/non-CHD
Kloster (14)	Denmark	1997-2014	Women with singleton pregnancies in Medical Birth Registry linked to National Patient Registry	3745 pregnancies	933 149	Simple, moderate, complex (ESC guidelines)	Preterm birth, SGA, educational level	HR preterm: simple 1.33, moderate 1.45, complex 3.26. Same pattern for SGA.
Opotowsky (15)	USA	1998-2007	US all-payer hospital admissions for vaginal or cesarean delivery	30 500 deliveries	42´571 606 Non-matched	Simple, complex (ACC Task force1, Warnes)	Combination of death, heart failure, arrhythmia, cerebrovascular accident, embolic events and unspecified cardiovascular complications.	OR 8.4 Compared to non-matched non CHD
Hayward (16)	USA (California)	2005-2011	Inpatient admission for delivery	3451 deliveries	3 638 590 Non-matched	Complex/ Non-complex (Marelli)	Cardiovascular arrhythmias, in-hospital mortality, heart failure, preeclampsia, length of stay neonatal preterm, mortality, morbidity. Longterm admissions	Higher OR for Preeclampsia (non-complex) Preterm, anemia, mortality (complex) heart failure, arrhythmia, growth restriction, re-admission.
Ramage (17)	Canada, except Quebec	2001-2015	Discharge Abstract Database, all hospitalizations.	2114 pregnancies	2´682´451 Non-matched	Anatomic and Clinical Classification of Congenital Heart Defects scheme, 10 lesion groups. Obstetric Comorbidity Index	Maternal Morbidity Outcome Indicator and Neonatal Adverse Outcomes Indicator. Mortality only during perinatal hospitalization.	Maternal morbidity aOR, 2.7, neonatal morbidity and mortality aOR, 1.8. Preterm birth varying between lesion groups.

AIMS

General

The overall aim of the thesis is to enhance pre-pregnancy counseling and care during pregnancy in women with congenital heart disease. The different papers correspond to frequently asked questions in the clinical situation.

The specific aims of the four studies in the thesis were

Paper I
To evaluate existing risk classifications in a single center cohort of pregnant women with congenital heart disease. We also studied the effect of maternal age on cardiac, obstetric and neonatal outcome in the same cohort. Our hypothesis was that the overall complication rate was acceptable, that advanced maternal age could contribute to increased risk and that the risk classifications were useful.

Paper II
To study the risk of cardiac complications during pregnancy (and two years of follow up) based on parity (number of pregnancies >12 gestational weeks) in a single center cohort of women with congenital heart disease. Our hypothesis was that women who were without cardiac complications during the first pregnancy were at low risk during a second pregnancy.

Paper III
To study cardiac, obstetric and neonatal outcome of pregnancy in women with congenital heart disease compared with matched controls using several national registries. Our hypothesis was that complication rates in CHD pregnancies would be lower in a nationwide register than in selected cohorts.

Paper IV
To define normal levels of heart biomarkers (NTproBNP and hs-cTNT) during pregnancy in healthy women (and relate to cut-off levels in non-pregnant women). Our hypothesis was that NTproBNP would increase during pregnancy but to a degree subdued by hemodilution. Hs-cTNT would not exceed cut-off levels for myocardial infarction.

PARTICIPANTS AND METHODS

The participants and study design of Paper I-IV included in the thesis are summarized below.

Table 5. Summary of the four papers included in the thesis

	Paper I	**Paper II**	**Paper III**	**Paper IV**
Study design	Prospective descriptive, single center	Prospective descriptive, single center	Retrospective national register-based cohort study	Prospective descriptive
Population	Pregnancies in women at the outpatient GUCH clinic, Gothenburg	Pregnancies in women at the outpatient GUCH clinic, Gothenburg	Women born 1953-1997. CHD diagnosis in the National Patient Register. First delivery, singletons. Matched controls.	Healthy women recruited from four maternal antenatal care units in the Gothenburg area.
Study period Data source	1997-2012 Medical and obstetric records of consecutive patients	1997-2015 Medical and obstetric records of consecutive patients	1997-2015 National registries: National Patient Register, Medical Birth Register, Cause of Death	2015-2017 Clinical, laboratory and echocardiographic data from serial measurements.
Number of included women/ pregnancies	232 women/496 pregnancies (including miscarriages and terminations)	307 women/580 pregnancies (including miscarriage >12 gestational weeks)	6´131 women with CHD, 158´343 matched controls with singleton delivery.	196 pre-pregnancy healthy women. Blood tests on four serial time points.
Objective	Performance of two risk classifications. Maternal age as covariate.	Cardiac outcome during and after pregnancy with parity status as covariate.	Nationwide data on maternal, obstetric and neonatal complications.	Estimation of normal levels of heart biomarkers and their variation within the same woman during pregnancy.
Cathegorization of CHD	CARPREG I and mWHO	CARPREG I and mWHO	ICD-10 code Q20−26, and corresponding ICD-7, -8 and -9 codes. Hierarchal categorization in 6 lesion groups	No CHD
Outcome	Cardiac, obstetric, neonatal complications	Cardiac outcome during each pregnancy and two years follow up.	Cardiac, obstetric and neonatal outcome during pregnancy and one-year postpartum.	95th percentile of heart biomarker levels. Comparison with existing cut-off levels for heart failure and myocardial infarction.
Statistics	Multivariate adjusted analyses that introduced either mWHO class or CARPREG score and age into the models.	Longitudinal model predicting outcome of 2nd to 1st and 3-8th to 2nd pregnancy. Multivariable logistic regression	Descriptive statistics on numbers and %. Odds ratio with 95% CI comparing CHD with non-CHD controls.	Repeated measures analysis of variance. Point-biserial correlation coefficients for cut-off values for biomarkers.

Study participants

Paper I and II

The study population consisted of consecutive female patients with adult congenital heart disease at the GUCH-center at Sahlgrenska University Hospital/Östra, Gothenburg, Sweden who were followed during pregnancy. The majority of patients have regular visits, not only during pregnancy, at the center. The women who became pregnant were prospectively registered. There are seven GUCH centers in Sweden; two of them tertiary centers with Gothenburg being one of the two. The catchment area is around 3.5 million inhabitants. We are aware that there are patients with congenital heart disease in Sweden that are lost to follow up in adult care and patients with simple lesions that may give birth at the local hospital without regular visits at a GUCH center. Still, we believe that patients from local hospitals with more severe/advanced heart disease are referred to us for evaluation and planning of pregnancy and delivery, as well as for pre-pregnancy counseling. GUCH Gothenburg have had regular multidisciplinary pregnancy conferences since 2008 and is located close to and in close collaboration with the obstetric clinic at Sahlgrenska University Hospital, which is the largest obstetric clinic in Sweden with approximately 10 000 births per year.

*Inclusion Paper I***.** All pregnancies 1997-2012 are included, also terminations and miscarriages. Data on pregnancy outcome including previous pregnancies, miscarriages and legal terminations were retrospectively collected from medical and obstetric records. A few patients with operated mitral stenosis were included since we did not know the genesis of the mitral valve disease. Both operated and non-operated patients were included. Patients with acquired heart disease or non-structural arrhythmia were excluded.

Inclusion Paper II. Women with pregnancies >12th gestational week 1997-2015 were included. The women in Paper I (n=232) are included in the 307 women in Paper II. Exclusion criteria were the same as for Paper I, and twin pregnancies.

Paper III

We used national health data registries held by the Swedish National Board of Health and Welfare (Socialstyrelsen) to identify women with a diagnosis of CHD and matched them with non-CHD women from the population by age at first birth and year of delivery. Swedish citizens have a unique personal identification number, which is changed to a de-identified code after linkage of registries to avoid identification of registries. Data linked to that individual can be searched within several different registers. It is mandatory for health care providers to report to health data registers. CHD women were found in the National Patient Register (NPR) where in-patient diagnoses (from 1964, full coverage from 1987) and out-patient diagnoses (from 2001) are registered. We included women who had reached an age of 15 years and had a registration in the Medical Birth Register (MBR, from 1973) for their first, singleton delivery. Women with a solitary diagnosis of patent ductus arteriosus not present above the age of three were excluded, since there is a high chance of spontaneous closure in the neonatal period.

Paper IV

Participants were recruited from four antenatal outpatient clinics in socioeconomically mixed areas in Gothenburg. A note in the waiting room at the antenatal outpatient clinic informed the pregnant women about the on-going study and if they were interested in participating, they received oral and written information and signed informed consent.

Participants were 201 healthy women without other medication than supplementation during pregnancy. Two women withdrew consent. We excluded two women with multiple gestation and one with previously unknown congenital heart disease from the final analysis. The blood samples from the women who had miscarriage were included. These women were later contacted and offered physical examination and echocardiography outside the study.

Methods

Paper I and II

At Sahlgrenska University Hospital there are two electronic medical record systems, one for medical and one for obstetric care, available for data collection based on every citizen's individual social security number. Previous cardiac surgery in childhood and adulthood, comorbidities, symptoms and signs of cardiac disease were found in the medical records. Antenatal data, outcome of previous pregnancies and detailed information on mode of delivery, complications and neonatal outcome were found in the obstetric records. Data on pregnancy outcome including previous pregnancies, miscarriages and legal terminations were retrospectively collected from medical and obstetric records. Miscarriage was classified as "early" if it occurred before 13 gw.

Classification of women in two risk classifications (CARPREG I and mWHO) was made retrospectively by three experienced GUCH cardiologists and double-checked by one of them. We chose not to analyze the more complex ZAHARA classification since it was found to be inferior to mWHO in a previous publication[188]. CARPREG II classification was not available at the time.

Paper I. We analyzed number of pregnancies and not women, why women who had corrective heart intervention between two pregnancies were calculated as one pregnancy with non-operated heart disease and one with operated heart disease. Outcome were cardiac, obstetric and neonatal events during consecutive pregnancies. Outcome definitions are reported in Paper I. We analyzed age as a covariate and dichotomized to ≤ or >35 years of age, a cut off often used in obstetric reports.

Paper II. We calculated number of women instead of number of pregnancies and chose a cut-off of 18 years, where non-operated were considered all women not operated before the age of 18. Miscarriages later than 12th gestational week were included in Paper II since the hemodynamic changes of pregnancy were considered to possibly affect maternal cardiac outcome. Outcome was cardiac complications associated with

each pregnancy and within two-year follow up. Outcome definitions are reported in Paper II. We analyzed the impact of previous pregnancy outcome on the next pregnancy.

Paper III

We used the National Patient register (NPR), Medical Birth register (MBR) to find cases with CHD and the Total Population Register (TPR) to find matched controls. Cases were characterized as having International Classification of Diseases (ICD)-10 diagnoses Q 20-Q 26 and corresponding classification codes in earlier ICD versions, ICD-7, ICD-8 and ICD-9. They were further classified into six major lesion groups in accordance with previous studies. Controls were matched for sex, age and year of first birth. Figure 1 in Paper III describe the selection of cases and controls. Maternal characteristics and previous chronic disease noted at the first antenatal visit in MBR was used.

Pre-specified cardiovascular, obstetric and neonatal outcome diagnoses were identified by ICD-8 to ICD-10 codes in the NPR and parameters in MBR. The date of cardiovascular outcome diagnoses was noted to evaluate if the outcome diagnosis also was present prior to the pregnancy. Data on outcome were collected from time of conception to one year postpartum. Mortality date was registered as in the Cause of Death register. The coverage and validity of the national registries are further described in Paper III. The observation time was 1973-2015, which was further separated into four eras, since health care systems, general health, diagnostics, coding of diagnoses, and panorama of disease may have changed over time.

Paper IV

The flowchart in Figure 6 show the time points when blood samples were drawn and health status was confirmed. Details on laboratory tests are described in Paper IV. Blood samples were hemoglobin, erythrocyte volume fraction, creatinine, and the heart biomarkers of interest; N-terminal Natriuretic Brain Peptide (NT-proBNP) and high sensitive cardiac Troponin T (hs-cTNT). Urine dipstick was used for ruling out renal disease, which might affect levels of biomarkers. If the blood test result was out of reference levels for non-pregnant persons, the women were contacted by phone and in some cases, supplementary blood samples were drawn or physical examination including echocardiography was performed.

There are several laboratory test for heart biomarkers, which are in use in different parts of the world. We chose the ones used in daily practice at Sahlgrenska University Hospital, Gothenburg, well documented and in use worldwide. We compared our findings with the cut-off levels used at the lab for ruling out heart failure (NTproBNP, <300 ng/l) or myocardial infarction (hs-cTNT <14 ng/l) in normal population and with the ESC guidelines proposed normal levels (NTproBNP <125 ng/l and hs-cTNT <5 ng/l). We analyzed the total cohort of pre-pregnancy healthy women. We identified a subgroup of women without obesity, levothyroxine supplement, or obstetric events and analyzed them separately.

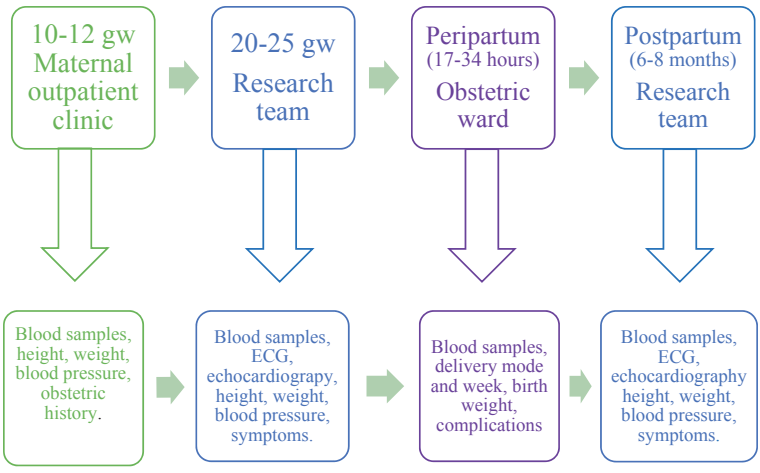


Figure 6. Flowchart of study protocol. gw = gestational week, ECG = electrocardiogram.

Statistical analyses

In *Paper I* we used outcome data from a single center cohort with number of pregnancies as denominator, not number of women. Descriptive data were numbers and percentages; for normally distributed parameters mean and standard deviation or for non-normally distributed parameters median and interquartile range as appropriate. The association between complications and the two risk classifications CARPREG I and mWHO was calculated with robust Poisson regression. Risk ratios (RR) and their 95% confidence interval (CI) were used as effect sizes. We reported the applicability of two risk classifications using sensitivity, specificity and area under the receiver operating characteristic (ROC) curve (AUC). An AUC of 1 indicates a perfect test, while 0.5 indicate no discriminative capacity. In general, an AUC of 0.7 to 0.8 is considered acceptable.

Paper II. Differences in cardiac complication across continuous variables (i.e., age and BMI at the first antenatal visit) were assessed with either the Student t test or the Mann-Whitney test (for non-normally distributed data). Categorical variables (i.e., smoking status, CARPREG and mWHO) were analyzed by utilizing Fisher's Exact test. For identification of cardiac complication outcome of subsequent pregnancy in relation to previous pregnancy odds ratios (OR) were calculated. In total three parity groups were compared (parity 1, 2, and ≥3). Three separate multivariable logistic regression analyses were used to detect variables predictive of cardiac complications. Significant predictors (i.e., CARPREG and mWHO score) were then used in a cross-lagged autoregressive longitudinal analysis predicting the OR of prior cardiac complication on subsequent cardiac complication controlling for CARPREG and mWHO score. A cross-lagged path indicates the prospective effect of one variable (e.g., CARPREG) on the other (e.g., cardiac complication).

Paper III. Descriptive statistics was used with numbers and percentages, mean and standard deviation. We calculated OR with 95% CI to estimate the difference be-

tween CHD women and non-CHD regarding complications during pregnancy from time of conception up to one year postpartum. The six lesion groups were analyzed in comparison with their matched controls. Statistical software used was R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

Paper IV. All continuous data were controlled for normality using the Shapiro-Wilk test. Mean-level changes in NTproBNP and hs-cTroponinT was examined across four time-points. In clinical laboratory literature, a minimum of 120 samples are required for statistical analysis[201]. Prior this analysis, the Shapiro-Wilk goodness-of-fit test showed that NTproBNP and hs-cTroponinT levels at each of the time-points were not normally distributed. Therefore, these data were log transformed before analysis of repeated measures analysis of variance (ANOVA). Point-biserial correlation coefficients for dichotomous variables were used for cut-off values of biomarkers. For significance testing independent T test and Mann-Whitney U test for continuous dependent variables and Fisher's Exact test for categorical variables were used. Differences in peripartum variables across cutoff values of NTproBNP and hs-cTroponinT were presented as mean ± Standard deviation (SD) or median ± interquartile range (IQR) as appropriate for continuous variables, and number with percentages for categorical variables. In addition, Bonferroni-adjusted comparisons were conducted for categorical variables by using adjusted standardized residual analysis for each cell in the table. Statistical significance at $p<0.05$ was assumed. IBM SPSS, version 26.0, statistical software (SPSS, Inc; Chicago, IL) was used. A statistician, in collaboration with the first author, performed the statistical analyses in Paper I, II and IV. The analyses for Paper III were performed by another statistician, in collaboration with the first author.

Ethical considerations

The Gothenburg Regional Ethical Review Board approved the papers. Patients at the GUCH center gave informed consent at the visit during pregnancy to use the medical and obstetric records for outcome data for Paper I and II. Data were registered according to Personuppgiftslagen (PUL1998:204, registration nr 29513) in transition to GDPR. The cohorts from Paper I and II were included in the ethical approval for Paper III. In Paper III, all personal identification numbers were removed by Swedish National Board of Health and Welfare and were replaced with a code. Due to ethical reasons, outcomes with less than five individuals in national registers are not presented. Participants in Paper IV signed informed consent. Pathologic findings rendered referral to suitable health care provider. Women who had a miscarriage after the inclusion were excluded from further study visits in Paper IV. They were contacted later and offered physical examination and echocardiography. The data are reported for groups of participants and not for individuals. The study participants in Paper IV received a letter after publication with information on the result in Swedish and a link to the publication. The four studies complies with the Declaration of Helsinki.

Ethical approval Paper I-III: 540-11, T974-12, T022-15, T544-16, T734-17, 2020-01178. Ethical approval Paper IV: 206-15, T114-16, T928-16, T746-17.

RESULTS

Paper I

The distribution of live birth, miscarriages, legal abortions and stillbirth according to CHD diagnosis is shown below (Paper I, Appendix, with permission from Elsevier).

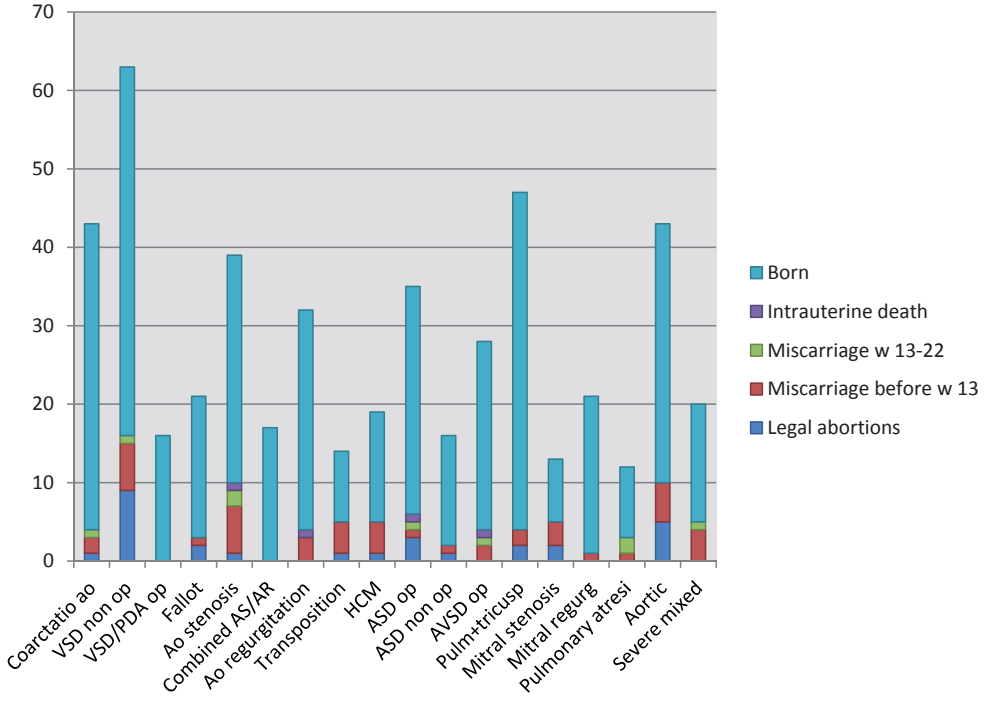


Figure 7. Distribution of legal abortions, miscarriages, intrauterine deaths and live birth (born). Total number of pregnancies on Y-axis. Ao, aortic. Combined AS/AR, aortic stenosis aortic regurgitation. HCM hypertrophic cardiomyopathy. AVSD, atrioventricular septal defect. Pulm+tricusp, pulmonary or tricuspid valve disease. Aortic, aortopathy.

Outcome data of the total cohort and of pregnancies in women below and above 35 years are shown in Table 6.

Table 6. Outcome of cardiac, obstetric and neonatal complications by age above or below 35 years in our single center cohort. (Paper I Table 2, with permission from Elsevier).

Outcome of pregnancies in women with congenital heart defects according to maternal age.

Complication (n = pregnancies with outcome data)	≤35 years n (%)	>35 years n (%)	Total n (%)	p-Value
Total complications (n = 471)[a]	169 (42)	38 (52)	207 (44)	
Cardiac complications (n = 463)[b]	50 (13)	15 (21)	65 (14)	0.054
Heart failure	14 (3.5)	5 (7)	19 (4)	
Arrhythmia	21 (5)	7 (10)	28 (6)	
Thromboembolic disease	2 (0.5)	0 (0)	2 (0.4)	
Syncope	3 (0.8)	0 (0)	3 (0.6)	
Maternal death	1 (0.2)	0 (0)	1 (0.2)	
Irreversible echo (n = 413)[c]	17 (5)	3 (4)	20 (5)	
Pregnancy complications (n = 468)[d]				
Early miscarriage	37 (9.3)	7 (9.8)	44 (9.4)	
Late miscarriage[e]	9 (2.5)	1 (1.6)	10 (2.4)	
Stillbirth[f]	5 (1.4)	0 (0)	5 (1.2)	
Obstetric complications (n = 412)[g]	45 (13)	12 (18)	57 (14)	0.989
Pregnancy-induced hypertension	5 (1.4)	2 (3.1)	7 (1.7)	
Preeclampsia	13 (3.7)	1 (1.5)	14 (3.4)	
Other (diabetes, cholestasis, oligohydramnios)	8 (2.3)	2 (3.1)	10 (2.4)	
Post-partum hemorrhage	25 (7)	8 (12)	33 (8)	
Neonatal complications (n = 417)[h]	51 (15)	11 (17)	62 (15)	0.665
Preterm birth (n = 408)[i, j]	26 (8)	7 (11)	33 (8)	
Small for gestational age[i]	19 (5)	2 (3.1)	21 (5)	
Low birth weight (<2500 g)[i, k]	23 (7)	3 (5)	26 (6)	
Cardiac birth defect [h]	11 (3.1)	1 (1.5)	12 (2.9)	
Other birth defect [h]	15 (4)	3 (5)	18 (4)	

Data obtained from medical and/or obstetric records. Of 397 pregnancies for age ≤ 35 years and n = 71 for age > 35 years, the figures have been adjusted for induced abortion, miscarriages, and stillbirth, according to type of complication, as follows: [a] 28 induced abortion excluded, three duplex pregnancies (resulting in six children) included; [b]three duplex pregnancies excluded from 471, five missing data; [c]three duplex pregnancies excluded from 471, 50 missing data; [d] induced abortions and three duplex pregnancies excluded; [e]44 early miscarriages excluded; [f]54 early and late miscarriages excluded; [g]three duplex pregnancies and 54 early and late miscarriages excluded from 471, two missing data; [h]three duplex pregnancies and five stillbirths included, 54 early and late miscarriages excluded; [i]three duplex pregnancies included, 54 miscarriages and five stillbirths excluded, four missing data; [j]iatrogenic prematurity (5/33) is included in Preterm birth; [k]small for gestational age is also included in Low birth weight when appropriate. The sum of subcategories can be higher than total number of complications because one pregnancy can have multiple complications. The P-value compares age above 35 with age up to 35 as reference.

When evaluating two risk classifications we found higher sensitivity with mWHO and higher specificity with CARPREG I. The area under the receiver operating characteristic curve (AUC) had values that are generally considered "good" for CARPREG I and "sufficient" for mWHO for cardiac complications.

Table 7. Appendix 3, Paper I (permission from Elsevier)

	Complication category								
	Cardiac			Obstetric			Neonatal		
	Sens %	Spec %	AUC	Sens %	Spec %	AUC	Sens %	Spec %	AUC
CARPREG score 0 vs 1–3	58	83	**0.71**	25	78	**0.52**	37	81	**0.59**
mWHO risk class 1 vs 2–4	86	44	**0.65**	68	44	**0.56**	64	44	**0.54**

Sens, sensitivity. Spec, specificity. AUC, area under the ROC curve.

Figure 2 a and b in Paper I show that complications do occur also in pregnancies with low scores of both classifications. When analyzing the cohort further we found that multiple complications could occur in the same pregnancy, Figure 8.

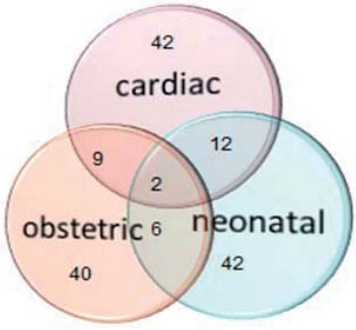


Figure 8. Distribution of complications.

Paper II

The odds ratio for cardiac complication outcome of the second pregnancy compared to the first was 5.47 (95% CI 1.76–16.94), adjusted for age, body mass index and smoking habits, if the woman remained in the same risk classification score. Figure 2 in Paper II is a flowchart of the cardiac outcome of pregnancies. Table 2 in Paper II show the risk classifications for women with and without cardiac complications. Standardized regression coefficients on the association between risk classifications

and cardiac complication at different parity time points were calculated in an autoregressive cross-lagged longitudinal model, adjusted for age, BMI and smoking. Standardized regression coefficients indicate how strong the association is between the directions of two parameters, from 0 to 1, where higher number is a stronger association. There was an association of the same outcome, i.e to have or have not a cardiac complication during the second pregnancy if there was, or was not, a cardiac complication during the first (standardized coefficient 0.38). There was no significant association of cardiac complications between second pregnancy and 3rd-8th pregnancy. CARPREG I score during the second pregnancy predicted cardiac complication at the 3rd-8th pregnancy (standardized coefficient 0.70), but not at the second pregnancy. There was no significant association between CARPREG I score the first pregnancy and cardiac complications the first or second pregnancy. There was no association for CARPREG I scoring between the second and third pregnancy, indicating that there was a change in score after the second pregnancy. Prior cardiovascular history is one parameter in that scoring system, and for example arrhythmia increase by time in the CHD population. There was no significant association between mWHO classification and first or second pregnancy cardiac complications. mWHO score at the 3rd- 8th pregnancy was associated with cardiac complication at the same pregnancies (standardized regression coefficient 0.50). The mWHO classification remained the same for every pregnancy, which is to be expected since it is based largely on type of lesion.

The follow up data on two years postpartum were without maternal deaths. During two years of follow up 13 of the 307 women had a heart intervention. Nine of them were ASD closures. Within two years, six women (1.9%) had heart failure and five of them were in high risk class (mWHO class III or IV) at their latest pregnancy.

Paper III

There were 6´131 women with CHD and 158´343 age-matched women without CHD in their first singleton pregnancy. The number of women with CHD who become pregnant has doubled from the first era (1973-1986) to modern era (2007-2015), see Table 1 Paper III. The proportion of severe CHD-diagnoses among them has also increased. Lesion class 6 (“other”) was the most common diagnostic group in the latest era followed by lesion class 4 (VSD). Lesion class 6 (“other”) include left-sided valvular disease, but the registries do not include information on degree of severity. Lesion class 5 (ASD) were 40% of the CHD in the earliest era which decreased to 18% in the latest era.

Lesion class 1 and 2, which are considered “complex”, were 5.9% of the CHD population in the earliest era to be compared with 8.1% in the latest era. During the same time age at first pregnancy increased. In the CHD cohort age increased from 22.6 to 27.4 years and the control population were matched for age. In the first era maternal mean weight at first antenatal visit was 60 kg in both cohorts, which increased to 67 kg in the latest era. Smoking decreased from 21% to 6%.

Cardiac complication rates were low in absolute numbers in both cohorts, however higher OR for CHD women (Paper III, Table 2). The cardiac complications in the non-CHD cohort were to a high degree “new onset” while it was more common for

CHD women to have had a complication before (Paper III, Figure 2a, b). All-cause mortality within 42 days postpartum was higher in CHD than in non-CHD, however, with low absolute numbers (Paper III, Figure 5).

The obstetric complications preeclampsia, gestational diabetes and postpartum hemorrhage were more prevalent in the CHD cohort, compared with non-CHD (Paper III, Figure 3). Previous miscarriage was also more frequent in the CHD cohort.

The neonatal complications were more prevalent in CHD pregnancies compared with non-CHD, as shown in Figure 5, Paper III. All studied parameters on neonatal complications (stillbirth, low birth weight, very low birth weight, small gestational age, preterm, very preterm and low Apgar score) had higher ORs in the CHD cohort.

Paper IV

The highest median levels of NT-proBNP were found in 10-12 gw samples. When dividing NTproBNP with EVF there was no significant difference between the four time points, indicating that the "concentration" of NTproBNP remains the same throughout pregnancy. The glomerular filtration rate is highest at 20-25 gw compared to the other time points, which coincided with the lowest NTproBNP levels. In the subgroup without any obstetric events, the 95th percentile was 155 ng/l, which is below the level used as cut-off for ruling out heart failure of 300 ng/l (Paper IV, Table 2 and Figure 2). Women with NTproBNP <125 ng/l at the peripartum measurement had higher glomerular filtration rate, had oxytocin only as postpartum hemorrhage prophylaxis and had more often spontaneous vaginal deliveries compared with women with levels >125 ng/l (Paper IV, Table 4). There were five women with NTproBNP levels above 300 ng/l on any occasion without signs or symptoms of heart failure. One outlier with 990 ng/l at the peripartum measurement had fever during delivery. She was contacted for physical examination and had repeated blood samples with normal findings. The highest levels of hs-cTNT were at the peripartum measurement. There were three women with hs-cTNT levels above 14 ng/l (range 14.4−30.6); two women with uncomplicated vaginal deliveries and one woman with fever (Paper IV, Table 3 and Figure 3). Time from delivery to blood test was associated with hs-cTNT >5.0 ng/l (Paper IV, Table 4). There were three women with preeclampsia and they had NTproBNP <125 ng/l on all four time points. Normal levels of NTproBNP and hs-cTNT during pregnancy, peripartum and postpartum are shown in Figure 9.

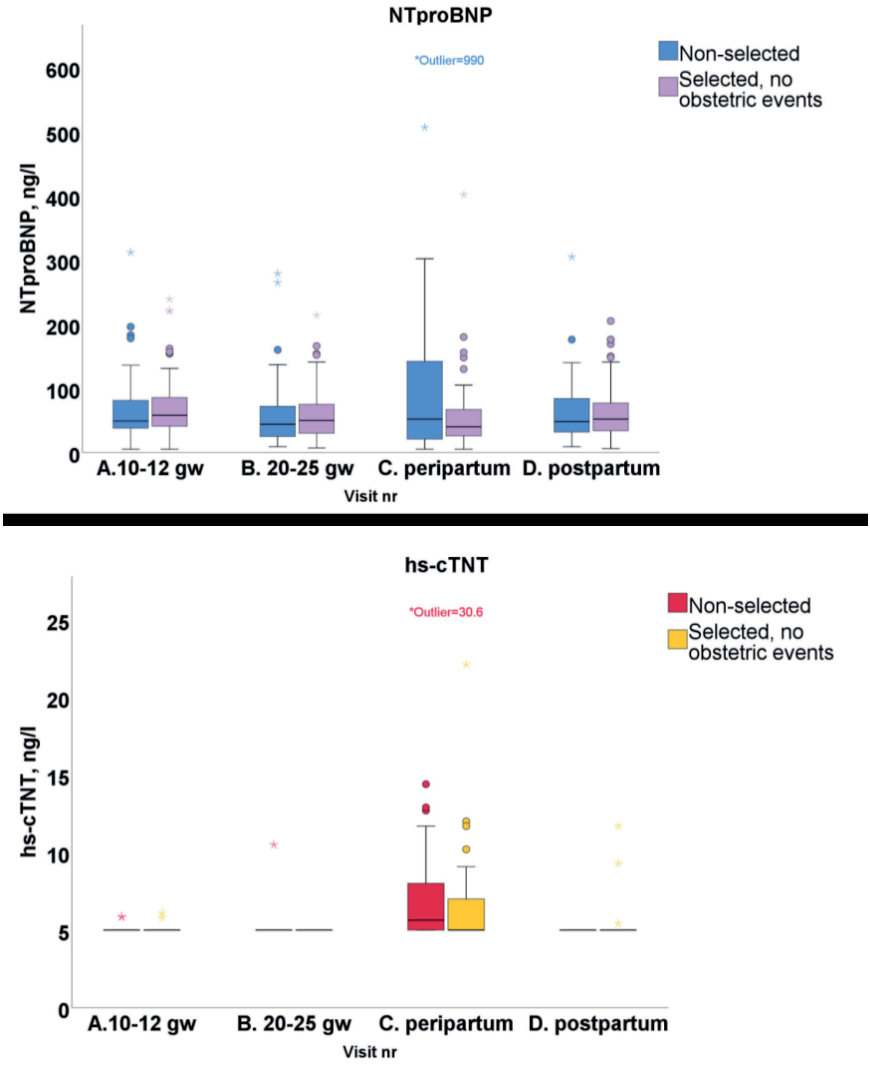


Figure 9. NTproBNP and hs-cTNT during pregnancy, peripartum and postpartum. "Selected" include women with spontaneous conception, BMI <35 at first antenatal visit, a normal pregnancy and delivery i.e. no miscarriage, no treatment with levothyroxine, no hypertensive disorders of pregnancy, not more than 1+ proteinuria on one occasion, and a vaginal non-assisted delivery at term without complications and no postpartum hemorrhage >1000 ml. Published with permission from BMJ Journals.

DISCUSSION

General discussion

Paper I, II and III address issues discussed in clinical practice. Young women with CHD ask questions about possible risks for themselves and their future children when considering pregnancy. We found the absolute risk of pregnancy-associated complications to be low and the use of risk classifications to be reasonable. If the woman had a first pregnancy without cardiac complications and if she still is in the same risk class there is a high probability that a second pregnancy will be uneventful.

Being single center studies (Paper I and II) the risk of misclassification of CHD diagnosis or outcome data is low. We cannot exclude the possibility of referral bias, which would indicate a lower risk among the general CHD population. In Sweden approximately 35 000 adults have a CHD diagnosis of whom 16 000 are included in the national SWEDCON register, indicating that they are regularly seen by a CHD specialist[3]. In different regions in the world, the proportion of CHD patients attending specialized care the rate may be even lower, depending on health care system and economic situation. However, the distribution of the study population includes both low- and high-risk classifications. In register studies (Paper III) there is a risk of misclassification of outcome diagnosis codes but that risk is the same for the entire study population. Validation studies of cardiac diagnoses in Swedish national registers have shown high validity[202, 203].

There are different rates reported in publications on pregnancy-associated complications depending on the methods of the studies. The spectrum of CHD diagnoses included in the reports affect outcome, as the cohorts are different in tertiary centers compared to primary centers. Patients often have multiple CHD diagnoses and sometimes a combination of CHD and acquired heart disease. Moreover, access to health care vary between countries and socioeconomic structures. Since there are many different CHD diagnoses, they are often categorized into a limited number of hierarchal classes, and the classification systems have different origin. Several publications report pregnancies both in women with congenital and with acquired heart disease. The definition of outcomes in different publications will further make comparisons difficult. Separating outcome as cardiac, obstetric and neonatal complications may overestimate the risk for the total population, since several complications can occur in the same woman. Sometimes number of women is reported in publications and sometimes number of pregnancies. When number of pregnancies is reported the same women may be included several times, which may affect the outcome depending on the study population. Absence of any complications is seldom reported, but is of interest for the patients.

Paper IV is a prospective study on heart biomarkers. The results are valuable in clinical practice if a previously healthy pregnant woman complains of chest pain or dys-

pnea. Elevated heart biomarker levels request further attention, but it is noteworthy that a handful of women had elevated levels without having a cardiac diagnosis. We did not investigate cut-off levels of biomarkers for the diagnosis of heart failure or myocardial infarction in pregnant women, but normal levels found in healthy women during and after pregnancy.

Paper I

Complications during pregnancy in a single CHD center

Paper I is a descriptive analysis of cardiac, obstetric and neonatal complications during pregnancy in a single center cohort. We found similar cardiac complication rates as in previous multicenter studies[133, 136, 151]. Heart failure was found in 4% to be compared with 1.6% in the ZAHARA study on 1´802 women in the Netherlands and Belgium with CHD, and 6.2% in the second ROPAC cohort and comparable with 4.1% in the first ROPAC cohort[133, 134, 136]. The ROPAC register include women from both low and high income countries and there is a possibility that centers include women with more complex disease at a higher degree than very simple defects, which may explain the differences. We found arrhythmia in 6%, which is similar to 4.7% in the ZAHARA cohort with a similar definition of arrhythmia as being clinically significant. In some studies ECG documentation or hospitalization for arrhythmia is required as the definition, why their reports of arrhythmia may be lower. Heart failure and arrhythmia are described in literature as more frequent from late second trimester to early postpartum[86, 134, 142]. We did not note the timing of complications. Thromboembolic events were rare (0.4%), not associated with mechanical valve prosthesis. In our cohort there was only one pregnancy with mechanical valve and few women were on more potent anticoagulation therapy than acetylsalicylic acid. Mechanical valve was found to be a risk factor in several publications for both mother and offspring[86, 133, 152, 204]. In our population, which was a medium risk population in a good-standard health care system, we had one maternal death (0.2%). Depending on study population there are reports of 0.6% to 2.7% maternal mortality with considerably higher risk in women with pulmonary arterial hypertension or Eisenmenger syndrome[136, 141, 175]. Cardiac complications are prevalent in the CHD population also without pregnancy, at increasing incidence by age[205-207]. However, non-pregnant CHD-women are not suitable as controls since they probably are a different cohort; younger, more symptomatic or with more complex disease, for example. Some of them are advised against pregnancy or choose not to become pregnant due to other medical risk factors.

The most common obstetric complication, besides miscarriage, was postpartum hemorrhage with 8%, which is at the same level as for our obstetric institution of 5-10%. Preeclampsia was found in 3.4% to be compared with 3% in the ROPAC, and 4.4% in the ZAHARA study[133, 136]. Udholm et al found preeclampsia to be more common in patients with an ASD diagnosis (not indicated whether they were operated or not) in a nationwide register study with 6.7% compared with 2.3% in control population. The ASD patients had more often become pregnant with assisted reproductive technology, which is a risk factor for preeclampsia[169].

The most severe neonatal complication is perinatal death. When excluding the perinatal death associated with maternal death, we found a perinatal death rate of 0.93%

after 22 gestational weeks, to be compared with 0.4% in the Swedish population. In the ZAHARA cohort, with exclusively CHD pregnancies, 3.8% stillbirth and infant mortality was found. They included deaths from 20 gw up to one year of age, which may be one explanation of their higher rate[25, 133]. Our rate of preterm birth (8%) was lower and low birth weight (6%) was lower or similar to other publications of 14-17% and 3.7-14% respectively[133, 151]. The familial recurrence rate of cardiac defects (2.9%) was not analyzed according to maternal diagnoses and we did not analyze the recurrence rate for paternal cardiac defects. The ESC guidelines reported higher rates and the difficulties with recurrence rate reports were discussed in the Introduction[67].

Maternal age

Advanced maternal age (in obstetric literature usually defined as age above 35 or 40 years) during pregnancy is associated with obstetric and neonatal complications in the general population[27, 208-211]. We found no significantly increased risk for cardiac, obstetric or neonatal complications in our cohort of CHD women above 35 years of age compared with 35 years or below. The group above 35 years comprised of 15% of the total cohort. When adjusting for mWHO class, age above 35 years had a relative risk of 1.07 (95% CI 1.01–1.14) for cardiac complications, but not for obstetric or neonatal complications.

Our analyses were made on composite outcomes. Cardiac complications increase by age in the total CHD-population that make the impact of pregnancy difficult to separate from the natural course. In accordance with our findings, the CARPREG II did not find maternal age to be predictive of cardiac event[135]. A Danish nationwide register-based study on CHD and controls separated age in 5-year intervals. The authors found age already from above 30 years to be associated with preterm birth and small for gestational age for both groups, with CHD women having an increased risk compared with non-CHD[196]. Since women 30-35 years were in the younger group in our study, it may have equalized the two groups. Maternal complications were not reported in the Danish study. There was a high correlation between maternal complication and offspring complication in the ZAHARA population ($r=0.85$, $p=0.002$[133]. One third of the neonatal complications in our study were in women with cardiac complications. CHD women were more often born preterm themselves in a Swedish nationwide register-based study and gave birth to preterm neonates, why genetic and other factors, besides age, may play a role in neonatal complications[179].

In conclusion, maternal age above 35 years per se was not a risk factor for adverse events during pregnancy in our cohort, but the risk for cardiac problems to occur increase by age in the CHD population.

Risk classifications

We tested the performance of two risk classifications (CARPREG I and mWHO) in our single center cohort[151, 187]. We chose not to evaluate the ZAHARA score, since it is more complex and was found inferior to mWHO by Balci et al in a CHD cohort[188]. We agree with the authors of the ZAHARA that the predictor “AV-valve regurgitation” is associated with poor ventricular function and may not be a predictor on its

own[133]. We found mWHO to have higher sensitivity and CARPREG I to have higher specificity for all complications, but the diagnostic accuracy was moderate for both classifications in assessing cardiac risk (CARPREG I 0.71 and mWHO 0.65). Evaluations of risk classifications in different cohorts have found mWHO to be better in predicting cardiac events[188-192]. Four of them were on CHD women exclusively while the Spanish study included 31% non-CHD. Wang et al compared CARPREG I, ZAHARA and mWHO in a meta-analysis and found CARPREG I to be inferior to the two others[195]. Van Hagen found mWHO to be moderately discriminative (AUC 0.71) and combining with pre-pregnancy history added prognostic value in the ROPAC register population[140]. CARPREG II, together with the three others, was evaluated recently in a CHD cohort of 100 patients and did not perform better than the others[194]. Balci et al found AUC <0.6 for CARPREG I, ZAHARA and mWHO for offspring risk, which was similar to our findings and indicate that these risk classifications have better performance for cardiac events.

The above-mentioned differences in selection of cohorts and definitions of outcome make evaluation of risk classification a challenge. A review on different risk classifications found that none of the classification systems has both high sensitivity and specificity and pointed out the methodological issues[193]. Using AUC is a way to measure performance of classifications and is a combination of sensitivity and specificity. Sensitivity, finding the ones with expected complications, may be the better measurement for planning health care service. Specificity, identifying presumably low risk pregnancies, may be more interesting for the individual counselling. All prevalent risk classifications are useful to some extent when giving advice to CHD women and when planning health care resources. However, the performances of the risk assessments are rather low and indicate the need for centralized expertise and experience as a complement. A reasonable approach is using a combination of risk classifications, with mWHO as a lesion-specific base, and predictors from CARPREG and ZAHARA in multidisciplinary conferences[40, 175, 193].

Paper II

Parity

The number of children that women give birth to will be influenced by many factors; socioeconomic, health care systems, inter-personal relations, own health issues among others. Maternal age and parity are naturally linked. We chose to include all pregnancies >12 gestational weeks. We classified women according to CARPREG I and mWHO and analyzed the effect of parity on cardiac complications during pregnancy. Age was not associated with cardiac complications, while high risk class was associated with unfavorable cardiac outcome. If the woman remained in the same risk class in the second pregnancy compared to the first, the age-adjusted OR was 5.5 (95% CI, 1.8-16.4) for the same cardiac outcome. Our results are similar to Gelson et al who found a lower proportion of cardiac complications in the second pregnancy compared with the first, however not statistically significant. They included 77 women with congenital and acquired heart disease without classifying in risk scores and 154 controls of similar age[212].

In large registry or multicenter studies parity is either not commented, or the women are dichotomized as being primiparous or multiparous[133, 135, 136, 140, 191]. Some publications separate parity into more than two categories[139, 151, 188, 190, 192]. However, none of the publications report an association between parity and cardiac outcome. Our data were collected retrospectively but during a certain time period. Primiparous women in our dataset might become pregnant again after data analysis, why the data cannot be interpreted as reproductive behavior in CHD women.

It is not surprising that women with an uncomplicated first pregnancy chose to become pregnant again. However, also women with cardiac complication chose to become pregnant again. There was an association between complication at the second pregnancy and change in mWHO class. A possible interpretation is worsening of ventricular function at the second pregnancy and change to higher mWHO class. Before every pregnancy, it is reasonable to assess whether the woman has changed risk class and need counselling accordingly. We analyzed the effect of parity in the total cohort; however, there might be lesions within the cohort where parity actually is a risk factor. We had few women with systemic right ventricle, women with poor systemic ventricular function and high-risk aortopathies for example, in whom parity might add to the progress of their lesion[159]. We did not analyze obstetric or neonatal complications. Maternal age seem to be more important than parity in publications on obstetric events in normal population[209-211]. In conclusion, CHD-women without cardiac complications during the first pregnancy can anticipate the same outcome of a second pregnancy if she is stable. The need for cardiac interventions within two years after pregnancy is low.

Paper III

Changes in maternal characteristics by time

In the time period from 1973 to 2015 the number of women with CHD who gave birth doubled. Survival in children with CHD has increased and when reaching adult age family planning become important[4-6]. Diagnostics of CHD has become better, with echocardiography in the 1990´s, why previously undiagnosed lesions can be found. We accepted women as CHD cases also when they got the diagnosis after pregnancy, since the defect was present during pregnancy. There may be women in the control population in the earlier eras who had an undiagnosed lesion, but since we accepted diagnoses found in the NPR also after pregnancy, we consider that risk to be low. Mean age at first CHD diagnosis in the cohort decreased during the period indicating that some of the women were diagnosed after pregnancy, especially in the earlier eras. The most common lesion in women giving birth in the earliest era was ASD. The proportion of ASD in the lesion groups decreased by time. The ICD code (Q21.1) for ASD is the same as for patent foramen ovale (PFO), which do not have hemodynamic impact. There may be women who got their ASD/PFO diagnosis after giving birth, at an older age. If the proportion of PFO in ICD-code Q21.1 is high, this would dilute the risk for hemodynamic complications.

In the earlier era only one fifth of the women had the CHD diagnosis before pregnancy which increased to 83% known CHD diagnosis before pregnancy in the latest era.

Late pregnancy assessment has been suggested to predict cardiac complications[135]. No prior cardiac intervention was associated with cardiac complications in the same study. In their cohort 53% of the women had a prior cardiac intervention while in our register cohort only 10% in the early, and 28% in the late era were intervened on. This suggests that their cohort was selected with more advanced CHD. Between 1973 and 2015 maternal age at first pregnancy and weight at first antenatal visit has increased, which is associated with obstetric and neonatal complications such as preeclampsia, PTB and SGA[91, 94, 95, 119, 196].

Swedish register data on cardiac complications in CHD pregnancy

The absolute risk of cardiac complications and maternal death were low, but compared with age-matched women the odds ratios were high, since cardiac complications are unusual in young women. For non-CHD women the cardiac complication mostly occurred as a new onset complication, while CHD women sometimes had experienced a cardiac complication before pregnany. Outpatient visits have been registered from 2001 and onwards why pre-existing diseases without hospitalization before that may be underreported, however we used both NPR and MBR for previous maternal diagnoses. The missing data would likely be similar for both groups. A Canadian discharge note register used a composite "maternal morbidity index" and found that CHD women more often had at least two previous morbidities compared with non-CHD. This index include previous cardiac disease why an association is to be anticipated[168].

Heart failure affected very few of the primiparous CHD-women during pregnancy in our cohort, which is far below numbers in single center and multicenter reports of 1.6-6.2%[133, 136]. During one-year follow up after pregnancy the absolute rate of heart failure was similarly low in both cohorts, however with higher OR in CHD vs non CHD women. Our missing data on follow up would be low in contrast to a Californian discharge-note register with 14% missing data on 30 days and 10% at one year[198]. In their study heart failure was reported in <0.5% of CHD during hospital stay. Most studies include both primiparous and multiparous women and multiparity is not considered to be a predictor for adverse outcome in guidelines. The multicenter studies ZAHARA and ROPAC and the Canadian discharge note register contain 45-50% primiparous women. Discharge note registers (without personal identification) and multicenter studies may contain several pregnancies in the same woman. A woman with previous diagnosis of heart failure is likely to be registered with heart failure diagnosis every pregnancy which could affect the reported outcome.

The Canadian register reported complications as a composite (Maternal Morbidity Outcome Indicator), where heart failure rate was not reported separately. An American discharge note register study found heart failure diagnosis in 0.96% of CHD women compared with 0.03% in non-matched non-CHD women[197]. The most common cardiac complication in their study was arrhythmia with 2.6% of CHD and 0.2% of non-CHD women. In our CHD cohort, less than one percent had arrhythmia during pregnancy, while just over two percent had a previous diagnosis of arrhythmia. There is a possibility in register studies that previous diagnoses will be registered even though they did not occur during the time of pregnancy and delivery. Maternal

all-cause mortality during pregnancy and 42 days postpartum in primiparous women is low in both CHD and non-CHD cohorts in a Swedish setting. In comparison, an American discharge note register found in-hospital maternal death of 0.15% in CHD women and non-adjusted OR 18.3[197]. The mortality rate may be even higher in areas with low health care services[21].

Swedish register data on obstetric and neonatal complications in CHD pregnancy

Preeclampsia was shown to be more common in ASD patients compared with controls in a Danish nationwide register study[169]. They found 6.7% of ASD women vs 2.3% controls with preeclampsia. Our preeclampsia rate was just under 5% vs 4% for CHD vs non CHD and the only lesion group with significantly higher OR was group 6 ("other"), not the ASD group. We did not adjust for ART in our study, which is associated with higher incidence of preeclampsia, while they found ART to be more common in ASD women compared with controls. When searching for causes of preeclampsia maternal cardiac disease has been proposed as a possible mechanism[213]. This mechanism cannot be confirmed by our study, since one would then expect much higher rates in CHD women. Gestational diabetes was twice as common in CHD compared with non-CHD. Gestational diabetes entails an increased risk of developing diabetes mellitus type II that is associated with morbidity and mortality[214, 215].

Preterm birth was studied in a Canadian register study where 13.9% in CHD women vs 7.4% in non-matched controls had singleton preterm birth <37 gw[168]. We had similar rates of preterm births as Josefsson et al, who found preterm birth in 8.7% of "simple" CHD compared with 6.2% in non-CHD. In their "complex" group, corresponding to our lesion group 1 and 2, 14.9% gave preterm birth, which is similar to our two lesion groups[179]. Low birth weight <2500 g had an OR above 1.0 in all our lesion groups, while mean birth weight was higher in CHD lesion group 2, 4 and 6 compared with controls. This indicates a variation between individuals within the lesion groups, which might be addressed by going into detail of the diagnoses, by adjusting for maternal comorbidities and for socioeconomic factors. Perinatal death was similar to the Canadian study (0.8% vs 0.2%), however they considered their numbers to be underreported[168].

The prevalence of cardiac malformations in the neonate was over four times as high in CHD women compared with controls in our study. We did not analyze if the cardiac malformation was the same as in the mother or if there were concomitant syndromes. Patients with autosomal dominant hereditary syndromes were not excluded. Oyen et al found a relative risk of recurrence of 3.4 to 79.1 depending on the first-degree relative´s cardiac defect, with an over-all relative risk of 8.15 (95% CI, 6.95-9.55) for the same heart defect phenotype[12]. The lowest risk of recurrence in our study was in the ASD lesion group and the highest in the conotrunchal lesion group.

In conclusion, women with CHD have higher probability of cardiac, obstetric and neonatal complications during pregnancy compared to women without CHD. However, the absolute risk for the total cohort is low.

Paper IV

NTproBNP during and after pregnancy in healthy women.

We studied a pre-pregnancy healthy cohort, to the best of our knowledge larger than reported before, with serial measurements of heart biomarkers during pregnancy, peripartum and at 6 months postpartum. Although cardiac output was higher in the second trimester compared with 6 months postpartum (5.6 vs 4.4 l/min, 27% change, unpublished data), NTproBNP levels were the lowest at the second trimester measurement. Hemodilution and glomerular filtration rate were the highest in the second trimester. We believe that this reflect the low NTproBNP levels seen in mid-pregnancy. The highest levels of NTproBNP during pregnancy were found in the first trimester with levels not significantly different from 6 months postpartum. The hemodynamic changes with hemodilution were reported in a systematic review to be increased by 8% in the first trimester and by 23% in the second trimester compared with non-pregnant reference levels[33]. In our study, EVF was 3% lower in the first, and 13% lower in the second trimester compared to 6 months postpartum. We did not measure third trimester levels of NTproBNP why comparison with other studies including third trimester cannot be done, but first and second trimester levels are comparable with others[42, 76, 77].

The peripartum measurements 17-34 hours after delivery can be compared with two previous reports on measurements 2-6 days and <48 h after delivery[42, 77]. Both found considerably higher levels of NTproBNP post-delivery with median 127 (5^{th}-95^{th} percentile 22-396) and median 107 (range 61-202) compared with our median 44 (range 5-990) in the total cohort. One difference between the two studies and ours was the rate of cesarean section, which was 47% in the Umazume and 33% in the Burlingame study, while our CS rate was 15%. Cesarean section (not specified whether acute or planned) was found to result in higher NTproBNP levels day 3 postpartum compared with vaginal delivery in a study on 78 healthy women[216].

A related biomarker, BNP, has been studied. No change in BNP levels between trimesters were found but sample size was low and the reference group were non-pregnant controls. All had BNP levels below a cut-off level of 100 ng/l for heart failure[80, 83]. When comparing BNP to NTproBNP the latter is more affected by renal function.

In our unpublished data of the total cohort we found mean EVF 0.36 in vaginal and 0.32 in CS deliveries. The volume shift patterns post-delivery may differ between vaginal and CS deliveries. NTproBNP levels in relation to EVF were stable, without significant changes during pregnancy, peripartum and 6 months postpartum, which indicate that a presumably higher NTproBNP production with increased cardiac output during pregnancy is balanced with hemodilution and increased glomerular filtration. Hopkins et al found a correlation between hypoxia (which cause high EVF) and elevated NTproBNP[68]. On the other hand, in a cohort of blood donors NTproBNP was lower with higher hemoglobin after adjusting for sex and age. EVF was not reported but was probably not elevated since the subjects were healthy, however only 3% were women aged 18-39 years[53]. One explanation might be that the NTproBNP levels were not adjusted for creatinine. Elevated creatinine, which would increase NTproBNP levels, is associated with low hemoglobin[217]. BMI increased between first and

second trimester, which could affect the levels of NTproBNP downwards. The weight change is caused by a combination of body fluid, fat and a growing fetus[218]. The relationship between NTproBNP and body composition has not been studied. In a study on BNP, high levels were associated with body weight changes during pregnancy and delivery[81].

Preeclampsia is a condition with endothelial dysfunction, vasoconstriction and hemoconcentration[84, 219]. NT proBNP is elevated in preeclampsia in most series compared to reference groups, which is presumed to be related to afterload increase[220-222]. In the study by Rafik et al there was no correlation with eGFR, while Seong et al found a strong correlation with creatinine and a negative correlation with hemoglobin[85]. There are studies on natriuretic peptides in pregnant women with heart disease. In a small study on seven women with dilated cardiomyopathy during pregnancy four of them had NTproBNP levels above 300 ng/l[223].

CHD studies have shown increased levels of NTproBNP in non-pregnant patients and in pregnant CHD patients BNP levels were higher than in healthy controls[65, 66, 82]. NTproBNP above 128 ng/l in 20 gw was associated with cardiovascular events during pregnancy in a CHD cohort. That level was derived as 95th percentile of pre-pregnancy healthy women from midwife centers, but the number of healthy controls were not reported. However, there was no comparison with pre-pregnancy levels and a majority of cardiovascular events affected patients with cardiac diagnoses where there might be elevated levels also in non-pregnant state, which makes interpretation difficult[86].

In our study there were five women with NTproBNP levels above 300 ng/l, none of which had cardiac complications. Levels above upper limit of normal of 125 ng/l were more common with 8-9% during pregnancy and 15% peripartum. Levels below 125 ng/l peripartum was associated with higher eGFR as expected, administration of oxytocin as postpartum hemorrhage profylaxis exclusively and spontaneous vaginal delivery. The NTproBNP upper limit of normal (95th percentile) in our selected cohort without events was 155 ng/l at 10-12 gw, 139 ng/l at 20-25 gw, 155 ng/l within 17-34 hours postpartum and 151 ng/l at 6 months postpartum which can serve as reference levels in similar populations. The cut-off level of <300 ng/l for ruling out heart failure is based on studies in older populations, including men, with a diversity of risk factors and chronic diseases and is not representative for our study cohort[48].

The sensitivity of NTproBNP for heart failure is high but the specificity is lower, resulting in patients with levels above 300 ng/l without heart failure[46]. On the other hand, patients with heart failure rarely have levels below 300 ng/l. Six blood samples in five women had levels above 300 ng/l in our total of 629 taken blood samples. The specificity was 99%, but sensitivity could not be calculated. In 60 blood samples, the levels were >125 ng/l resulting in a specificity of 90%. The majority of elevated levels were at the peripartum measurement when there was no echocardiography performed, but medical history and physical examination 6 months postpartum revealed no clinical signs of heart failure. We find it acceptable to use the cut-off level of 300 ng/l knowing that it may result in extended blood samples and echocardiography in few cases.

Troponins during and after pregnancy in healthy women

There are few reports on Troponin I and cTNT during pregnancy and delivery[42, 78, 79]. In our study 0.6-2% of the blood samples during pregnancy and 6 months postpartum were above 5 ng/l, which is the cut-off used for normal levels at our lab. On the other hand, at the peripartum measurement (17-34 hours post-delivery) 55% had levels above the cut-off, which was associated with time from delivery to blood sample. There was no significant association with eGFR or delivery mode. In a study on TNI (not hs-TNI) in 51 women during labor and 24 h postpartum, the maximum level was found 24 h post-delivery. In that study, 20% had oxytocin as labor augmentation and 90% were vaginal deliveries. None had TNI levels above cut-off[79]. Umazume et al also found significantly elevated hs-TNI levels post-delivery 2-6 days compared with first trimester levels. There was a significant difference between vaginal deliveries with higher hs-TNI levels compared with levels in CS[42]. There was no information if all CS in the Umazume study were elective.

We did not find a statistical difference between delivery mode and hs-cTNT above and below 5 ng/l. We included both elective and emergency CS as well as assisted vaginal deliveries in the "other" group as opposed to spontaneous vaginal delivery. Some of them were in active labor before CS, which could affect the levels. Physical activity can increase the levels of hs-cTNT and thereby make the difference between groups less pronounced[74]. cTNT and cTNI was studied in a cohort of women with normal pregnancy or hypertensive pregnancy at 36 gw compared with non-pregnant women. There was no statistical difference in troponins between non-pregnant women and pregnant women, while preeclamptic women had higher levels[78]. We had no samples from the third trimester but the Umazuma study found somewhat elevated levels of hs-TNI during the third trimester compared with the first (median 1.3 vs 0.8 ng/l). One month postpartum the median was 1.2 ng/l, still higher than first trimester, which indicate that pregnancy per se not is associated with elevated troponins. This is in accordance with our 6-month visit when 2% had levels above 5 ng/l. The relevance of elevated biomarkers 6 months postpartum has not been investigated, but our physical examination including echocardiography and symptoms reported by the participants revealed no overt pathology.

Oxytocin is used both as labor augmentation and as postpartum hemorrhage prophylaxis. ST-depression on Holter-ECG within 3 minutes after administration of two different doses of oxytocin in CS as prophylaxis has been reported[224]. The authors found an association with ST depression and chest symptoms with the higher bolus dose of 10 units (16.7 µg) compared with 5 units (8.3 µg). TNI 24 h post-delivery were not statistically different between the groups. We found no statistically significant difference with the use of oxytocin and hs-cTNT above or below 5 ng/l. There was a non-significant difference in hs-cTNT >5 ng/l (43% vs 25%) for women receiving labor augmentation oxytocin, which may be related to prolonged labor, i.e. physical effort.

Three women had hs-cTNT levels above 14 ng/l at the peripartum measurement which is set as cut-off below which myocardial infarction is unlikely. None of them had signs or symptoms by medical records of myocardial ischemia; however, ECG or

echocardiography were not performed at that measurement. All of them had fullterm spontaneous vaginal deliveries and none had renal insufficiency (the lowest eGFR was 84 ml/min/1.73). One of them had fever but otherwise none had complications, hemoglobin within normal, one had epidural anaesthesia, there was one in each of the three oxytocin groups and birthweights were 3475-3700 g. The 95th percentile of hs-cTNT at the peripartum level was 12 ng/l and the specificity was 99.5% of all samples (3/628) and 97.5% at the peripartum measurement (3/119), why we mean that the existing cut-off of 14 ng/l is reasonable. In conclusion, existing cut-off levels of heart biomarkers NTproBNP and hs-cTNT can be applied to rule out cardiac cause in pregnant women with symptoms of dyspnea or chest pain.

Clinical implications

With increasing number of pregnancies in women with both congenital heart disease and acquired heart disease, dedicated multidisciplinary collaboration and units have started. The GUCH/ACHD center in Gothenburg started multidisciplinary conferences on pregnancy in women with congenital heart disease in 2008. The multidisciplinary collaboration preferably should include cardiac, anesthetic and obstetric competence with the possibility to engage other disciplines when needed.

Pre-pregnancy counseling, planning visits during pregnancy and delivery as well as contraception issues are important in women with congenital heart disease[40, 225-227]. Using risk classifications together with information on comorbidities and functional testing form the basis for counseling. Adding additional predictors to the mWHO classification is recommended in the ESC guidelines[175]. We did not find maternal age to be associated with cardiac complications. However, the risk for cardiac complications (and concomitant change in risk score classification) increase by age in CHD population. Advanced maternal age is associated with obstetric and neonatal complications in the literature, even if we did not find significant associations. If the woman had a previous pregnancy, we can anticipate the same cardiac outcome if her risk classification still is the same.

Decreased heart rate response during exercise and pre-pregnancy cardiopulmonary exercise test with maximum oxygen uptake below 25 ml/kg/min has been associated with unfavorable maternal and neonatal outcome[228, 229]. Exercise testing indicate if cardiac output can increase, as in pregnancy, without symptoms. Heart biomarkers may add to the assessment of pregnant women. There are few publications on biomarkers in pregnant women with CHD[82]. NTproBNP levels >128 ng/l at 20 weeks of gestation was associated with cardiovascular events[86]. Knowing normal changes of heart biomarkers during pregnancy indicate which changes might be anticipated during pregnancy in CHD women, especially if pre-pregnancy levels are known.

In the care for CHD women issues on reproduction and pregnancy need to be addressed regularly. Imaging, testing of physical performance and identifying cardiac and obstetric risk factors should preferably be done before pregnancy and subsequently be re-evaluated. Since there are no perfect risk classifications, the dedicated multidisciplinary team need to contribute with expertise and experience of cardiac, anesthetic and obstetric problems that might occur during pregnancy. Written plans

for follow up during pregnancy and after delivery, plan for the delivery with individualized cardiac, anesthetic and obstetric aspects are needed to assure the safest possible care for mother and child.

Strengths and limitations

Paper I. Strengths of the study is access to medical and obstetric records. Congenital heart diagnoses, previous cardiac complications, number of previous pregnancies and miscarriages are reliable data. Outcome of pregnancy and neonatal complications were also easily accessible. Categorizing in CARPREG I and mWHO-classification was done by one author, why all participants were classified in the same manner.

Limitations are the proportion of women above 35 years (15%) when comparing age above and below. In obstetric literature 35 years is a frequently used cut-off when analyzing obstetric and neonatal outcome, but there is no agreed age suitable for comparison of cardiac outcome. Dichotomizing age might lead to undetected outcome within other age ranges. We analyzed composites of cardiac, obstetric and neonatal complications. One of the parameters within a composite might be statistically significant, however undetected among the composite group. We chose to not evaluate the ZAHARA classification, however it is the only classification based on CHD women exclusively. CARPREG II classification was not available at the time.

Paper II. Strengths of the study were access to data from the same women in repeated pregnancies, with risk classifications continuously updated between every pregnancy and very low missing data on cardiac outcome. Other authors have reported parity, but mostly in terms of primiparous or multiparous participants. Patients with a previous successful pregnancy want to know the chances of a successful second pregnancy, which cannot be answered by that type of categorization. Another strength is two-year follow up after pregnancy, since the literature on prognosis after pregnancy is scarce.

Limitations were missing data on smoking habits and BMI why adjustment in the analysis was unsatisfactory. The aim was to study cardiac complications, why obstetric and neonatal odds ratios were not reported. The number of participants with multiple pregnancies >2 was too small to evaluate the outcome of the third to eighth pregnancies separately, why they were analyzed as one group.

Paper III. Strengths are the population based design with large nationwide registries and personal identification numbers used when linking between registers which ascertain that we obtained data on the correct individual. National data during many years generate a large number of participants and controls that make comparison between CHD and non-CHD reliable. There is no selection of participants depending on access to care, since public financed health care is available to all Swedish citizens. The validity of cardiac diagnoses in NPR and obstetric data in MBR is acceptable[203, 230-232]. Personal linked data entail the possibility to find the first time an ICD-code was registered and analyze if a condition was present before, during or after pregnancy.

Limitations are changes during the studied time period in cardiac and obstetric care, health status in the population, ICD-code systems and validity of parameters which

may have changed during the time studied. The gestational week for inclusion in the MBR changed 2008 from 28th gestational week to 22nd, why stillbirth and maternal death in early pregnancy might be underreported in the earlier time period. However, data on all live birth pregnancies are reliable and both CHD and non CHD are reported in the same way. Diagnoses in outpatient care were not reported until 2001 why cardiac and obstetric events handled without hospitalization might be underreported before that. ICD-codes do not contain information on the severity of the diagnosis, which is better studied in single- or multicenter studies or in disease-specific registries. Categorizing in lesion groups inevitably lead to conclusions on the whole lesion group while information on subgroups might be lost. A diagnosis with high event rate might be evened up with a low event rate diagnosis within the lesion group.

We analyzed all cause maternal death during pregnancy and one year postpartum using the date of death from the Cause-of-death register, but have not analyzed the actual cause. We did not analyze if there were differences in emigration during follow up between CHD and controls, but we have no belief that the cohorts would differ (approximately 0.4% of women emigrate per year). We did not adjust for socioeconomic variables, which is possible to do by linking to other registers. There may be other unmeasured and unknown confounding factor not taken into account. The cohort was primiparous women with singleton pregnancies, why outcome is not representative for multiple pregnancies or multiparous women.

Paper IV. Strengths of the study are among others that the women were their own controls since, for example, BMI and renal function affect levels of biomarkers. This is the first study to analyze hs-cTNT and the largest in analyzing NTproBNP in pregnancy. Another strength is the physical examination including echocardiography to verify that the participants were healthy. We reported a cohort of pre-pregnancy healthy women, but also a subgroup of normal-weight women without any obstetric events. There are different heart biomarkers in use in different parts of the world and we choose to analyze the ones in use at our hospital. The participants were recruited from different socioeconomic areas at the antenatal clinics.

Limitations of the study are possible bias towards recruiting women with an interest in health issues having the time to come to appointments, women with worries about the pregnancy or women with familial cardiac problems. We do not have access to the number of participants who denied participation. The majority were of Caucasian ethnicity why our results should be interpreted with caution in other parts of the world.

Main findings

Women with CHD had higher probability of cardiac, obstetric and neonatal complications during pregnancy than non-CHD women. The absolute risks reported in registries were low, but compared with controls all three adverse outcomes were elevated. The CHD-diagnosis pattern, as well as health status parameters, changed from 1973 to 2015.

Our single center cohort of CHD women had higher risk of complications during pregnancy than what was found in nationwide registries. However, this Swedish single-center data on risks were comparable with international literature.

Maternal age above 35 years was not associated with adverse outcome during pregnancy. There is a known increase in cardiac complications by age in all CHD patients, but pregnancy was tolerated well also in women above 35 years.

Two risk classifications (CARPREG I and mWHO) were acceptable, but not good, in predicting complications during pregnancy in our single center cohort.

There was a high probability that the second pregnancy had the same maternal cardiac outcome as the first pregnancy in women with CHD. However, change in risk classification group between the pregnancies affect the probability. There were few cardiac interventions during two-year follow-up after pregnancy.

The biomarkers NTproBNP and hs-cTNT levels during pregnancy and peripartum in pre-pregnancy healthy women were below the levels when heart failure or myocardial infarction should be suspected.

FUTURE PERSPECTIVES

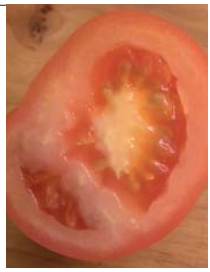
Further national register studies could evaluate the short- and long-term effects on pregnancy-related complications in women with CHD. CHD as a group is diversified and some diagnoses might be more susceptible for future morbidity than others. The registers contain data on rare diagnoses that are difficult to find in adequate numbers to evaluate in single- or even multicenter studies. We found the majority of pregnancies in women with CHD to be without severe complications, but when complications occur, it may affect both mother and offspring. Thus, it is important to further evaluate separate, rare CHD diagnoses. With national register data, there is low risk of selection bias. Validation of CHD diagnoses and outcome data is valuable for future research.

Comparing regime of operations between men and women with the same CHD diagnosis and operation technique would also be possible from nationwide registers. Choice of valve substitute, timing of interventions for example and thereby prognosis could differ between the sexes.Prediction of complications are philosophically difficult, since we are biased from start and chose factors that we think are important, and then analyze them. Using artificial intelligence to find possible predictors is tempting, especially since we have access to big data and the research team are familiar with the methods. We might find previously unknown predictors to add to current knowledge.

However, national registers held by The Swedish National Board of Health and Welfare cannot give detailed cardiac information on severity of valve stenosis, degree of cyanosis or ventricular dysfunction, while obstetric data are easier to obtain. Linking to the SWEDCON register could give contribution with more detailed information on the CHD characteristics and severity of diasese. The ROPAC register, collect and report detailed information on pregnancy in women with congenital and acquired heart diseases and is ongoing. Since several years, there is a Nordic collaboration between CHD-centers. The countries have similar health care systems and registers, why collaboration is reasonable to get solid data and large numbers. So far, none of the Nordic projects has addressed pregnancy.

Pre-pregnancy evaluation using cardiopulmonary exercise tests in combination with biomarkers and early postpartum assessment after vaginal and CS deliveries would be useful to confirm (or reject) the few previous studies on these themes. The relationship between cardiac performance and utero-placental blood flow has been studied and would be interesting to further describe. Cyanotic conditions, Fontan circulation and women with aortopathies would be of special interest to further understanding of hemodynamics in CHD pregnancy. There are no qualitative studies on how CHD women experience pregnancy-related symptoms; how to separate normal pregnancy symptoms from worsening of the heart condition. Guidelines recommend pre-pregnancy counseling because as physicians, we think it is our duty to inform about possible consequences but there is little knowledge on how the information is perceived[233]. We have had multidisciplinary conferences with a written plan for delivery in Gothenburg since more than a decade. Still, there is no evaluation of adherence and effectiveness of the conference and no comparison with other CHD centers.

PERSONAL REFLECTIONS



During almost twenty years of work with CHD-patients. I am used to get questions that have no obvious answers. The search for knowledge, to get ideas, make hypotheses, discuss with colleagues and draw conclusions is even more satisfying when the result can be translated into clinical practice. I am privileged to have the opportunity to search for answers to some of the questions I got during the years from young women in the beginning of a long journey. It is as important to give reassuring advice to low-risk patients as to identify high-risk patients, plan for the best outcome and be prepared to advise against pregnancy. In pre-pregnancy counselling there is a need of profound knowledge of the individual´s diagnosis and hemodynamic situation as well as obstetric considerations, why multidisciplinary collaboration is essential. I am fortunate to work in that kind of environment.

The unanswered questions have the same potential as a seed; it may fall into soil with the appropriate mix of nutrients (research team, university, funding), start to grow and prosper (colleagues and supervisors) and finally give fruit (results and answers).

Within that fruit there are numerous of new seeds….

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