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Mode of Delivery and Pregnancy Outcome in Women with Congenital Heart Disease

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Content

1 Introduction

1-1 Congenital heart disease: etiology and epidemiology

Congenital heart disease (CHD) is the leading cause of birth defects [Richards 2010], making up 28% of congenital defects in infancy [Ntiloudi 2016]. Heart development is completed in the first trimester of pregnancy, with the key period of heart development and consequently of a possible embryologic maldevelopment being the time between two and eight weeks of pregnancy [Liu 2015]. Causes for cardiac malformation can be differentiated into environmental and genetic factors, with a far bigger share being assumed of the latter.

Known environmental factors include fetal exposure to rubella or substantial alcohol levels, as well as maternal insulin-dependent diabetes mellitus [Gelb 2015].

The genetics of CHD remain a subject of ongoing research. Early on, aneuploidy and microdeletions were found to be associated with CHD. While the majority of patients with CHD does not have other anomalies, other anomalies and identified syndromes, respectively, are associated with CHD in 25 to 40% of cases [Richards 2010]. Chromosomal anomalies are associated with CHD in 30% of cases. A third of the patients with Turner syndrome, i.e. a missing X chromosome in females (45,X), and half of the patients with Klinefelter syndrome, i.e. an additional X chromosome in males (47,XXY), are also affected by CHD. In patients with trisomies, 50% of patients with Trisomy 21, 80% of patients with Trisomy 13 and nearly all patients with Trisomy 18 are also affected by CHD. With regard to microdeletions, 75% of patients with DiGeorge syndrome, i.e. 22q11.2 deletion syndrome, and 50 to 85% of patients with Williams-Beuren syndrome, i.e. 7q11.23 deletion syndrome, are also affected by CHD. In recent times, it has become possible to identify single genes responsible for common syndromes associated with CHD like Marfan's syndrome, which is caused by a defect of the Fibrillin 1 (FBN1) gene, or Noonan syndrome, which in 50% of cases is caused by a defect of the Protein Tyrosine Phosphatase, Non-Receptor Type 11 (PTPN11) gene, the remaining 50%

most likely being caused by defects in other genes involved in the Ras signaling pathway like the KRAS, RAF1 and SOS1 gene. Additionally, single genes responsible for isolated, i.e. non-syndromic, CHD have been discovered, like the NKX2.5, GATA4 and MYH6 genes, mutations of which are causing atrial septal defects, or the NOTCH1 gene, mutation of which is responsible for aortic valve malformations such as bicuspid aortic valve and early aortic valve calcification.

However, it should be noted that the vast majority of CHD arises sporadically and specific genetic defects can be identified for few affected individuals only [Gelb 2015].

With regard to the epidemiology of CHD, an epidemiological change of great impact can be observed [Ntiloudi 2016]. A few decades ago, CHD was considered a pediatric disease due to the small number of patients with severe lesions surviving into adulthood [Perloff 2008]. Excluding infectious diseases, CHD still is the main cause of death during the first year of life globally [Richards 2010]. In the western world, advances in cardiac surgery and congenital cardiology have changed this pattern drastically. While in 1940, 90% of patients with complex CHD died well before reaching adulthood, nowadays the survival rate to the age of 18 is greater than 90% [Stout 2005]. Depending on severity of CHD and possible status after surgical repair, life expectancy can correspond to life expectancy of the healthy population.

A study including almost 7000 adult congenital heart disease (ACHD) patients in England showed the most common causes of mortality in this patient group to be chronic heart failure (42%), pneumonia (10%) and sudden cardiac death (7%) [Ntiloudi 2016].

The precise incidence and prevalence of CHD is difficult to estimate for a variety of reasons. First, an echocardiographic assessment of all newborns worldwide is not performed. In 1971, a prospective study conducted in the United States of America that included over 56.000 births showed an overall incidence of congenital heart disease of 8.14 per 1000 total births (stillbirths and live births) [Mitchell 1971]. In 2012, a whole-population screening by color Doppler ultrasound conducted in Tianjin, China, that included over 90.000 births even reported an incidence of 20.0 per 1000 live births [Liu 2015].

Secondly, a different regional distribution of prevalence of CHD has been reported, with a maximum of 9.3 per 1000 live births in Asia and a minimum of 1.9 per 1000 live births in Africa [Ntiloudi 2016]. However, apart from genetic differences that seem to account for a different regional distribution of CHD subtypes, missed diagnoses are likely to play a role in this fairly large difference of overall prevalence [Ntiloudi 2016].

Additionally, it has to be noted that up to 90% of small ventricular septal defects close spontaneously within the first year of life [Ntiloudi 2016], and that a large number of simple heart defects such as atrial septal defects or patent ductus arteriosuses remain unnoticed by the patients [Ntiloudi 2016]. Some of these asymptomatic heart defects may turn symptomatic due to the increased physical strain of a later pregnancy, thus leading to a belated diagnosis [Ouzounian 2012].

Lastly, another limiting factor for collecting comparable data is the ongoing discussion on which heart defects to include as congenital in studies on CHD (see 2-3.1).

The overall prevalence of CHD worldwide is approximately 8 to 9 per 1000 live births [Ntiloudi 2016]. The most common heart defects – making up approximately half of all congenital heart defects – are septal defects, i.e. ventricular septal defects with an incidence of 2.62 per 1000 live births and atrial septal defects with an incidence of 1.64 per 1000 live births [Ntiloudi 2016]. The prevalence of ACHD is approximately 3 to 6 per 1000 adults [Ntiloudi 2016]. Recently, higher life expectancy in CHD patients has led to ACHD patients outnumbering pediatric CHD patients. The Canadian registry on the prevalence of ACHD showed an increase of 54% during the period of 2000 to 2010 reaching 6.12 per 1000 adults in 2010 [Ntiloudi 2016]. Adults made up 54% of the total CHD patient population in 2000 and 66% in 2010, with a percentage of 49% and 60%, respectively, in the total population of patients with severe CHD [Ntiloudi 2016].

1-2 Congenital heart disease and pregnancy

As mentioned above, advances in cardiac surgery and congenital cardiology have led to an increasing number of patients with CHD reaching childbearing age, including women who develop the desire to become pregnant. Thus, a completely new and steadily growing patient collective in need of consultation and treatment with regard to pregnancy and delivery has emerged in the past decades, posing a challenge for cardiologists and obstetricians alike [Kaemmerer 2012].

Previously, women with CHD were often advised against pregnancy [Stout 2005], but this has changed due to a likewise increasing experience with this relatively new patient collective. Risk evaluation and counseling is now conducted individually, based on underlying physiology and heart function [Stout 2005, Kaemmerer 2012].

In its guidelines on the management of cardiovascular diseases during pregnancy from 2011, the European Society of Cardiology (ESC) names maternal heart disease as the major cause of maternal death during pregnancy in western countries [Regitz-Zagrosek 2011]. According to the World Health Organization, 99% of all maternal deaths occur in developing countries, with hemorrhage and infections as the most frequent causes [Say 2014]. In total, 0.2 to 4% of all pregnancies in western industrialized countries are complicated by cardiovascular diseases, with the numbers increasing [Regitz-Zagrosek 2011]. Hypertensive disorders being the most frequent cardiovascular events during pregnancy worldwide, occurring in 6 to 8% of all pregnancies, the most frequent cardiovascular disease is dependent on region. In non-western countries, rheumatic valvular heart disease comprises 56 to 89% of all cardiovascular diseases in pregnancy [Regitz-Zagrosek 2011]. In western industrialized countries, rheumatic valvular heart disease has declined heavily after the introduction of penicillin against streptococcus infection. As a result, CHD has become the most frequent cardiovascular disease present during pregnancy in western countries, comprising 75 to 82% of all cardiovascular diseases in pregnancy. Outside of Europe and North America, CHD represents no more than 9 to 19% of cardiovascular diseases in pregnancy [Regitz-Zagrosek 2011].

Although ACHD patients seem to tolerate pregnancy much better than patients with valvular or ischemic heart disease [Roos-Hesselink 2013], maternal complications occurring during pregnancy as well as during and after delivery in women with CHD have been described. The most frequent cardiac complications during pregnancy in women with CHD are arrhythmias, occurring in up to 4.5% of pregnancies [Karamermer 2007]. The time at which most women with CHD are likely to encounter cardiac complications is in the third trimester and after delivery [Cauldwell 2016]. Heart failure is the most common cardiac complication during delivery, occurring in up to 4.8% of pregnancies [Karamermer 2007]. Postpartum hemorrhage (PPH) has been described as the most severe obstetric complication, occurring in 3.0% [Siu 2001] to 8.4% [Karamermer 2007] of pregnancies. Additionally, premature delivery (15.9%) and small for gestational age (8.0%) have been described as the most common obstetric complications in women with CHD [Karamermer 2007].

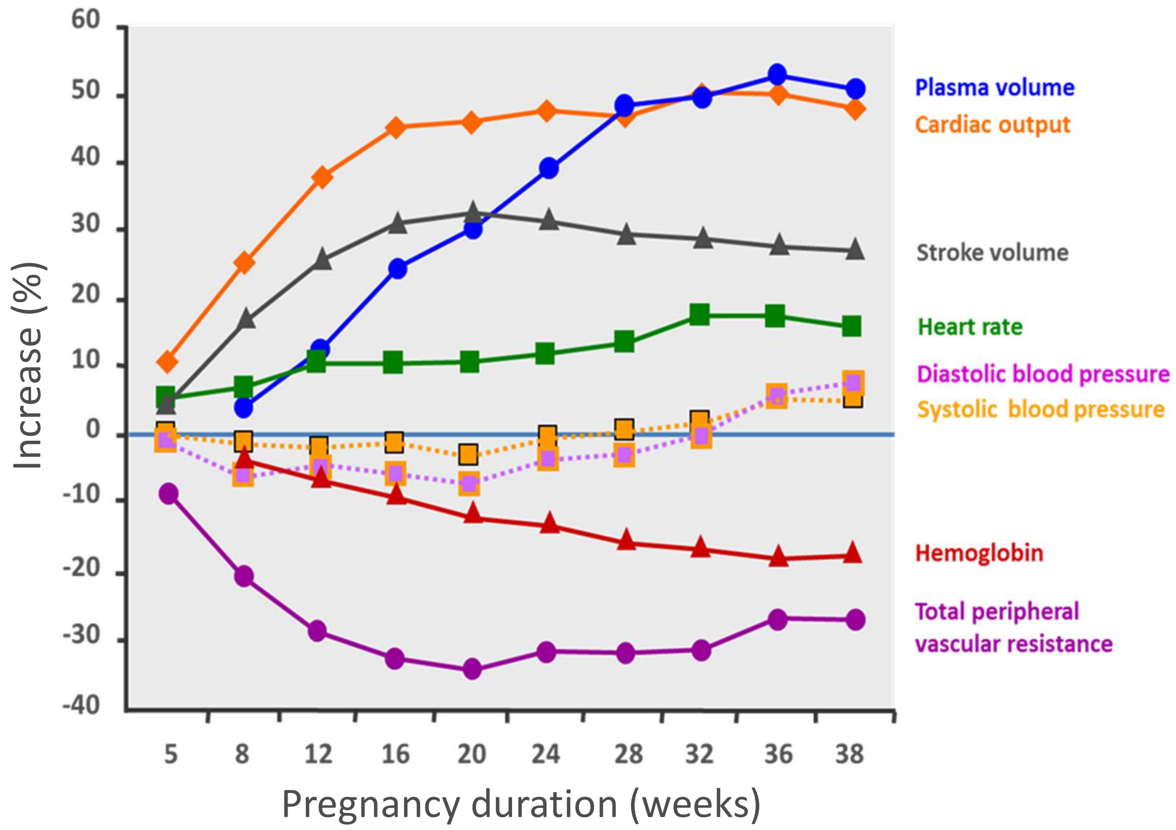
1-3 Physiological changes during pregnancy and delivery

1-3.1 Physiological changes during pregnancy

Even in healthy women, hemodynamic changes caused by pregnancy are a challenge for the female body and the cardiovascular system especially. Physiological changes during pregnancy are shown in Figure 1.

In order to ensure an adequate uteroplacental perfusion which in turn secures an adequate supply of nutrients and oxygen to the developing fetus, the maternal cardiovascular system adapts to pregnancy initially with a decline in total peripheral vascular resistance of up to 40%

Figure 1. Physiological changes during pregnancy (modified after: Karamermer 2007).



of pre-pregnancy levels [Karamermer 2007]. While cardiac afterload is reduced due to the decrease in total peripheral vascular resistance, cardiac preload increases by the continuous increase in cardiac output of up to 50% of pre-pregnancy levels [Ouzounian 2012]. As a mode of compensation, maternal heart rate increases by 10 to 20 beats per minute [Kuschel 2016a]. Blood pressure typically decreases early in gestation, reaching a nadir by midpregnancy, and returns to or even exceeds pre-pregnancy levels by term [Ouzounian 2012].

To compensate the decrease in diastolic blood pressure caused by the decrease in total peripheral vascular resistance, blood volume increases by 1.0 to 1.5 liter, i.e. 30 to 50% [Karamermer 2007]. A minor increase in erythrocyte mass in relation to plasma volume is responsible for a physiological anemia and lower blood viscosity in pregnant women [Karamermer 2007].

All these physiological changes can lead to subjective constraints such as fatigability, shortness of breath, vertigo, edema, palpitations, arrhythmias and syncopations even in healthy women [Kuschel 2016a].

In women with CHD, evaluation of the ability or the lack of ability to compensate the higher cardiovascular demands during pregnancy is of special concern. It is crucial for an adequate counseling with regard to contraception and advice in favor or against pregnancy [Stout 2005, Kaemmerer 2012, Koerten 2016].

It should be noted, however, that the risk for cardiovascular complications during pregnancy and delivery in women with CHD differs significantly based on the severity and the subtype of heart defect.

The aforementioned 30 to 50% increase in intravascular volume and cardiac output that occurs in normal pregnancy by early to mid-third trimester is poorly tolerated in patients whose cardiac output is limited by obstruction, myocardial dysfunction or valvular lesions, and may result in congestive failure. Thus, congenital heart defects leading to left heart obstruction such as aortic and subaortic stenosis, respectively, bicuspid aortic valve and coarctation of the aorta seem most problematic. Pregnancy may also result in ascending aortic aneurysm or dissection in patients with an anatomic predisposition such as Marfan's syndrome or Ehlers-Danlos syndrome [Karamermer 2007].

According to the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for cardiovascular disease during pregnancy, high-risk lesions are defined as left-sided heart obstructions, severe left ventricular function, pulmonary hypertension, cyanotic heart disease and mechanical protestic valves [Karamermer 2007]. The ZAHARA (Zwangerschap bij Aangeboren HARtAfwijkingen) study has identified presence of mechanical valve prosthesis and severe left heart obstruction as risk factors for cardiovascular complications [Drenthen 2010]. Risk for heart failure is higher in patients with left-sided lesions in comparison with right-sided or repaired cyanotic lesions [Ruys 2014a].

1-3.2 Physiological changes during delivery

After the physiological changes during pregnancy, delivery poses an additional and especially intense challenge for the cardiovascular system of the pregnant woman.

In the first stage of labor, cardiac output increases up to 30% [Ouzounian 2012]. In the second stage of labor, cardiac output increases up to 50% because of pushing efforts [Ouzounian 2012]. A single contraction pushes 300 to 500 milliliters (ml) in the vascular periphery, thus increasing blood pressure, cardiac output and heart rate [Kuschel 2016b]. Fear and pain may increase cardiac output additionally by activating the sympathetic system [Ouzounian 2012].

During the actual delivery, radical shifts of volume are occurring rapidly. Delivery of the newborn causes a decompression of the vena cava. Within minutes, the weight of the uterus decreases many times. Contraction of the uterus causes a shift of blood into the arteries' periphery, resulting in a relatively sudden blood loss [Kuschel 2016b]. Blood loss differs in vaginal delivery and Caesarean section, respectively. In vaginal delivery, blood loss up to 500 ml is considered normal, in Caesarean section up to 1000 ml, with amounts equal or greater being considered as hemorrhage [Cornette 2013, Cauldwell 2016]. In a recent study on hemorrhage in women with CHD, Cauldwell et al. describe a mean blood loss of 439 ml in spontaneous vaginal delivery in comparison with 715 ml and 722 ml in use of forceps and secondary Caesarean section, respectively [Cauldwell 2016].

Apart from these direct cardiovascular changes, the physical burden of delivery also depends on the anesthesia that is being used. While most women undergoing Caesarean section under epidural anesthesia remain stable hemodynamically, Caesarean section under spinal anesthesia is associated with significant cardiovascular changes [Ouzounian 2012]. Since the effect of a sympathetic block is greater in spinal anesthesia, vasodilatation and hypotension may result. In the aforementioned study by Cauldwell, general anesthesia is associated with the highest mean blood loss of 854 ml [Cauldwell 2016].

1-4 Mode of delivery in women with congenital heart disease

The question of which mode of delivery is suited best to reduce the cardiovascular burden of birth is of special importance in women with CHD. There seem to be arguments in favor of and against both vaginal delivery and Caesarean section. While there is less cardiac stress in vaginal delivery, it generally occurs unplanned and is of unpredictable length. In Caesarean section, on the other hand, there are more profound changes in shorter time, more anesthesia, a risk of bleeding at least twice as high as in vaginal delivery as well as a higher risk of infection, thrombosis and repeated Caesarean section in consequent pregnancies. However, it can be planned, i.e. a cardiologist can be present, and it is a short procedure.

Due to the lack of experience with the relatively new patient collective of pregnant women with CHD, until recent times official guidelines did not exist and decision on mode of delivery was largely based on expert opinion [Robertson 2012, Ruys 2014b]. While women with CHD were commonly advised against pregnancy before [Stout 2005], the current ESC guidelines on the management of cardiovascular diseases during pregnancy only advise against pregnancy in the case of pulmonary hypertension, oxygen saturation below 85% at rest and in patients with transposition of the great arteries and systemic right ventricle or Fontan patients who are significantly limited in their physical strain [Regitz-Zagrosek 2011].

Clinical experience has shown over the years that many women with CHD tolerate vaginal delivery well [Robertson 2012]. The current ESC guidelines on the management of cardiovascular diseases during pregnancy advise for vaginal delivery in asymptomatic patients with moderate or good ventricular function [Regitz-Zagrosek 2011]. Cardiologists in general recommend vaginal delivery as mode of choice for women with CHD, considering the significant cardiovascular changes at Caesarean section – i.e. the significant and sudden changes of pressure, resistance and volume in the venous, arterial and pulmonary arterial system – to be of greater impact in favor of vaginal delivery than the predictable short length and possible presence of a cardiologist might be in favor of Caesarean section.

However, while many recent publications have recommended vaginal delivery as mode of choice for women with CHD [Karamermer 2007, Robertson 2012, Ruys 2014b], Caesarean section rate remains higher in these patients than in the normal population [Opotowsky 2012, Ruys 2014b, Thompson 2015]. With Caesarean section rate among women with CHD varying widely between countries, Germany ranks above international average [Ruys 2014b].

1-5 Objectives of the present thesis

As mentioned above, rate of Caesarean section remains higher in women with CHD than in the normal population despite general recommendation of vaginal delivery. In Germany, a Caesarean section rate above international average can be observed.

The objectives of the present single-center study were to collect obstetric data on women with CHD who had previously delivered at the Klinikum rechts der Isar, Munich, and to perform in-depth analysis of the birth process to be able to compare mode of delivery, pregnancy outcome as well as indications for Caesarean section and induction of labor between women with and without CHD. Answers to questions regarding the statistical relation between mode of delivery and pregnancy outcome, type of heart defect and risk for Caesarean section, among others, shall be provided.

Results from one of the large centers in Germany and internationally with regard to delivery in women with CHD may help to ascertain the reasons for the comparatively high Caesarean section rate among women with CHD altogether and in Germany, respectively.

2 Materials and methods

2-1 Study design

The present study was designed as a review of and follow-up study to a study conducted by Constanze S. Pawelczak on patients with CHD from the German Heart Centre Munich (Deutsches Herzzentrum Muenchen) who had delivered at the women's clinic (Frauenklinik) of the Klinikum rechts der Isar, Munich, between 1998 and 2008 [Pawelczak 2014].

Making use of the ViewPoint database that has been introduced at the Frauenklinik, Klinikum rechts der Isar, Munich, in the year 2005, the study design of the present study involved (a) reviewing data of those patients from the former study who had delivered at the Klinikum rechts der Isar, Munich, between 2005 and 2008, with the objective to partly include new parameters that had not been analyzed in the previous study, and (b) collecting new data on all CHD patients from the German Heart Centre Munich who had delivered at the Klinikum rechts der Isar, Munich, between 2009 and 2013.

The present study is a monocentric historical cohort study, i.e. a retrospective data collection and analysis based on patient files.

In a historical cohort study it is analyzed retrospectively what kind of incidences occurred comparing a group of patients exposed to a possible risk factor and a group of patients not exposed to a possible risk factor for said incidences. In the case of the present study, the patient cohort is defined as pregnant women. Accordingly, CHD is the supposed "risk factor" for the so-called "incidences" of Caesarean section, poor pregnancy outcome etc.

A historical cohort study is not to be confused with a case-control study, in which it is analyzed retrospectively whether or not there had been an exposure to a possible risk factor for a disease, comparing a group of patients with said disease – the so-called "case group" – and a group of patients without said disease – the so-called "control group".

The study design consisted in (a) data collection on planned parameters of women with CHD who delivered between 2005 and 2013 at the Klinikum rechts der Isar, Munich, (b) performance of a threefold matching with women without CHD who delivered during the same period of time at the Klinikum rechts der Isar, Munich, and (c) a comparison and statistical analysis of planned parameters on mode of delivery and pregnancy outcome, among others.

Parameters were decided upon in collaboration with the supervisor of the present study, Priv.-Doz. Dr. med. Bettina Kuschel, Head of the Section of Obstetrics and Perinatology at the Frauenklinik, Klinikum rechts der Isar, Munich.

The present study was conducted as part of a collaboration between the Frauenklinik, Klinikum rechts der Isar, Munich, and the German Heart Centre Munich. The German Heart Centre Munich is one of the large centers in Germany and also internationally with regard to the treatment of pregnant women with CHD. Patients with CHD are treated at the German Heart Centre Munich since birth and childhood, respectively. Those of the female CHD patients of the German Heart Centre Munich who became pregnant and delivered between 2005 and 2013 at the Klinikum rechts der Isar, Munich, were identified comparing patient files of the German Heart Centre Munich and the Klinikum rechts der Isar, Munich.

Data collection on patients with CHD was performed reviewing patient files of the Frauenklinik, Klinikum rechts der Isar, Munich, and the German Heart Centre Munich, both in electronic and handwritten form. Data that had previously been entered in the corresponding fields in the computer software program ViewPoint was analyzed electronically. A more in-depth single-case analysis could be conducted reviewing the handwritten protocols of birth processes with comments by obstetricians, midwives and nurses alike. Conducting a case-to-case review of doctor’s letters from the German Heart

Centre Munich concerning the patients with CHD who delivered between 2009 and 2013, more specific data was available on certain cardiologic parameters in these patients (for details on collected data see 2-3).

To guarantee an individual threefold matching, follow-up pregnancies, i.e. the birth of a second or third child in the same patient within the observation period, were excluded from the study. Also excluded were abortions since one of the main objectives of the present study was to collect and compare data on mode of delivery.

Patients with CHD provided written consent to participate in the study.

Once the process of defining and identifying the CHD patient collective that was to be included in the present study was finished, a threefold matching was carried out using the four parameters year of delivery, gravidity, parity and age of mother at delivery.

Year of delivery was used to eliminate a statistical impact of possible changes in obstetric management over the course of the study. With the same clinic director being in charge between 2005 and 2013, practice patterns were consistent and differences or changes in obstetrical management were performed only in accordance with current guidelines at the time.

The three maternal qualities gravidity, parity and age of mother were used to guarantee an equal distribution and thereby eliminate a statistical impact of known risk factors for Caesarean section and poor pregnancy outcome, respectively [Heffner 2003].

Gravidity was defined as the number of times the patient has been pregnant. Parity was defined as the number of times the pregnancies were carried to a viable gestational age. Age of mother at delivery was recorded in full years of age, calculated from date of birth of the mother and date of birth of the child.

Following the matching process, data collection on patients without CHD was performed using the computer software program ViewPoint.

The study protocol was approved by the Ethics Committee of the Klinikum rechts der Isar, Medizinische Fakultaet, Technical University of Munich, on December 20, 2013 (ethical approval number 433/13).

2-2 Study population

In accordance with the study protocol of the present study, all patients with CHD from the German Heart Centre Munich that delivered between 2005 and 2013 at the Klinikum rechts der Isar, Munich, were to be included in the present study. In 2010 and 2012, two patients with CHD delivered directly in the German Heart Centre Munich because of their high-risk profile. Since both the German Heart Centre Munich and the Klinikum rechts der Isar, Munich, are institutions of the Technical University of Munich with the same obstetricians from the Frauenklinik, Klinikum rechts der Isar, Munich, being in charge at delivery, these two patients were also included in the present study.

Using the computer software programs SAP and ViewPoint, it was possible to search the totality of patient records of the Frauenklinik of the Klinikum rechts der Isar, Munich, for correspondences with the patient records of patients with CHD of the German Heart Centre Munich. Data showed which of the CHD patients were in obstetric treatment at the Klinikum rechts der Isar, and whether they had actually delivered at the Frauenklinik, Klinikum rechts der Isar, Munich, or just received screening measures such as ultrasound.

Between 1998 and 2008, 192 pregnant women with CHD were registered in the Outpatient Department for Adults with Congenital Heart Defects at the Department of Pediatric Cardiology and Congenital Heart Defects of the German Heart Centre Munich (Ambulanz fuer Erwachsene mit angeborenen Herzfehlern des Deutschen Herzzentrums Muenchen). Of these 192 patients, a total of 79 patients with CHD were scheduled for a delivery at the Frauenklinik, Klinikum rechts der Isar, Munich. Seven pregnancies were terminated early by abortion. In accordance with the study protocol of the previous study by Pawelczak, patients who aborted were excluded from the study. The remaining 72 patients carried out a total of 82 deliveries. Eight times the same patient delivered twice during the observation period, one patient delivered three times during the observation period. In accordance with the study protocol of the previous study, these ten follow-up pregnancies were excluded from the study. In total, 72 deliveries from 72 patients were included in the previous study by Pawelczak. Of the 72 deliveries occurring between 1998 and 2008, 47 occurred between 2005 and 2008. In accordance with the study protocol of the present study, these 47 deliveries only were included in the present study.

Between 2009 and 2013, another 203 pregnant women with CHD were registered in the Outpatient Department for Adults with Congenital Heart Defects at the German Heart Centre Munich. Of these 203 patients, a total of 80 patients with CHD were scheduled for a delivery at the Frauenklinik, Klinikum rechts der Isar, Munich. One pregnancy was terminated early by abortion and exluded from the study in accordance with the study protocol of the present study. The remaining 79 patients carried out a total of 90 deliveries. Nine times the same patient delivered twice during the observation period, one patient delivered three times during the observation period. In accordance with the study protocol of the present study, these eleven follow-up pregnancies were excluded from the study. In total, another 79 deliveries from 79 patients were included in the present study.

Uniting the patient population of 47 from 2005 to 2008 and the patient population of 79 from 2009 to 2013 amounted to a total of 126 patients as the patient population of the present study.

A threefold matching was carried out using the matching parameters year of delivery, gravidity, parity and age of mother at delivery. For four of the 47 women with CHD that delivered between 2005 and 2008, as well as for six of the 79 women with CHD that delivered between 2009 and 2013 – equaling a total of ten women with CHD who delivered between 2005 and 2013 – a threefold matching could not be carried out due to missing matches in women without CHD.

Thus, 43 women with CHD who delivered between 2005 and 2008, and 73 women with CHD who delivered between 2009 and 2013 were included in the present study – equaling a total of 116 women with CHD who delivered between 2005 and 2013 (see Figure 2). The threefold matching that was carried out amounted to a total of 348 women without CHD who delivered during the same period.

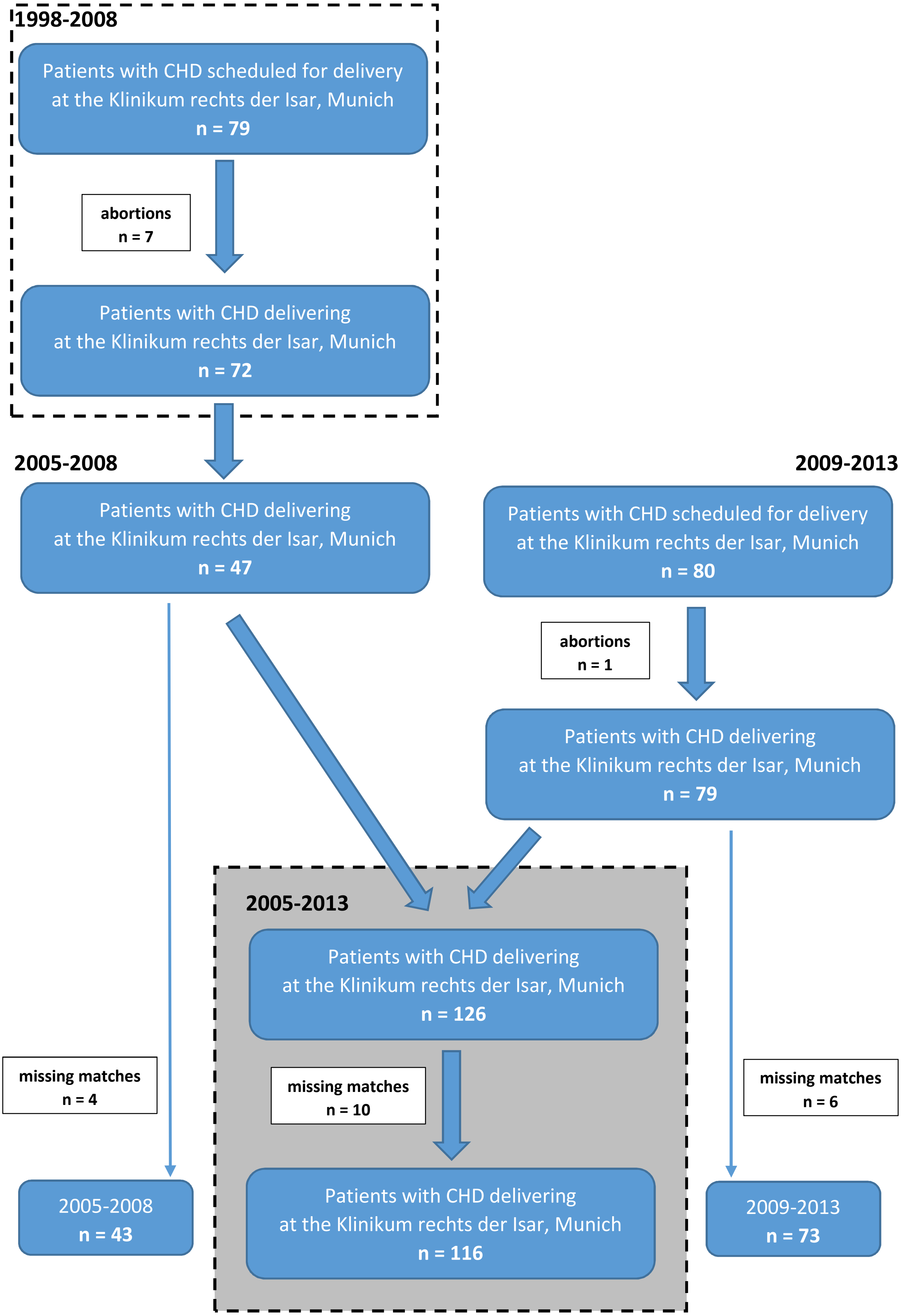
2-3 Data

2-3.1 Cardiologic data

The cardiologic data that was collected as part of the present study includes data on diagnosis of heart defect, group of heart defect, severity of heart defect and heart function. Said data was collected for all CHD patients, i.e. for the 43 patients from the previous study by Pawelczak who delivered between 2005 and 2008 and for the 73 patients who delivered between 2009 and 2013. Additionally, for the group of patients with CHD who delivered between 2009 and 2013, data was collected on status post intervention, blood oxygen level, presence of Fontan circulation, presence of a right system ventricle, presence of pacer, presence of implantable cardioverter defibrillator (ICD) and presence and nature of a possible artificial heart valve.

Data on diagnosis of heart defect was collected based on an individual review of the patient's file and the doctor's letters regarding the patient in collaboration with Prof. Dr. Dr. Harald Kaemmerer, Head of the Outpatient Department for Adults with Congenital Heart Defects at the Department of Pediatric Cardiology and Congenital Heart Defects of the German Heart Centre Munich. Professor Kaemmerer performed identification and classification of heart defects.

Figure 2. Composition of the study population.



A total of 20 different heart defects was identified in the patient population. In presence of combined diagnoses, primary main cardiac diagnosis was decisive.

The 20 heart defects found were further subgrouped into the following eight groups: post-tricuspid shunts, pre-tricuspid shunts, left heart obstructions, right heart obstructions, complex anomalies, hereditary, congenital rhythm anomalies and other (see Table 1).

Table 1. Groups of heart defects (left) and single heart defects (right).

Post-tricuspid shunts	Ventricular septal defect
Pre-tricuspid shunts	Atrial septal defect Patent foramen ovale
Left heart obstructions	Aortic stenosis Bicuspid aortic valve Coarctation of the aorta Subaortic stenosis
Right heart obstructions	Double outlet right ventricle Pulmonary stenosis Tetralogy of Fallot
Complex anomalies	Congenitally corrected transposition of the great arteries Tetralogy of Fallot with absent pulmonary valve Truncus arteriosus Transposition of the great arteries
Hereditary	Marfan’s syndrome
Congenital rhythm anomalies	Atrioventricular block
Other	Aortic aneurysm Ebstein’s anomaly Congenital form of hypertrophic obstructive cardiomyopathy Mitral valve prolapse

There is an ongoing discussion on which heart defects shall be included as congenital in studies on CHD patients [Perloff 2008, Ntiloudi 2016]. Patients with Marfan’s syndrome were

included in the present study in accordance with the literature such as Karamermer et al. [Karamermer 2007] or Balint et al. [Balint 2010]. However, since Marfan's syndrome is excluded in other occasions because of it being rather hereditary – i.e. genetic without manifestation of the disease at birth – than congenital, Marfan's syndrome was subgrouped as "hereditary" to leave the possibility to exclude it in any analysis of the data in the future.
Patients with only patent foramen ovale or mitral valve prolapse were included in the present study in accordance with the literature such as Warnes et al. [Warnes 2001] that classify "isolated patent foramen ovale" and "isolated congenital mitral valve disease" as simple congenital heart disease.

Data on severity of CHD was collected applying the classification of the American College of Cardiology (ACC) [Warnes 2001]. Heart defects were differentiated into the three groups of simple, moderate and severe heart defects (see Table 2). In cases of combined diagnoses, primary cardiac main diagnosis was decisive for classification. Heart defects were classified clinically, i.e. depending on the size of the defect, for example, the same type of heart defect could be either simple or moderate. This applied to ventricular septal defect, atrial septal defect, aortic stenosis and pulmonary stenosis. All other heart defects belonged to a single group of severity only. The classification was performed by Prof. Dr. Dr. med. Harald Kaemmerer based on an individual review of the patient's file and doctor's letters.

Data on heart function was collected applying the Congenital Heart Disease Functional Classification of the University of California, Los Angeles (UCLA), after Perloff [Perloff 2008], which differentiates heart function in four classes according to physical capacity of the patient (see Table 3). On each patient's visit at the Outpatient Department for Adults with Congenital Heart Defects at the German Heart Centre Munich, heart function was evaluated. Heart function after operation or catheter based treatment as evaluated last before delivery

Table 2. Severity of single heart defects (after: Warnes 2001).

Simple	Aortic stenosis Atrial septal defect Bicuspid aortic valve Congenital atrioventricular block Mitral valve prolapse Permanent foramen ovale Pulmonary stenosis Ventricular septal defect
Moderate	Aortic stenosis Aortic aneurysm Atrial septal defect Coarctation of the aorta Congenital form of hypertrophic obstructive cardiomyopathy Ebstein's anomaly Marfan's syndrome Pulmonary stenosis Subaortic stenosis Tetraloy of Fallot Ventricular septal defect
Severe	Congenitally corrected transposition of the great arteries Double outlet right ventricle Tetralogy of Fallot with absent pulmonary valve Transposition of the great arteries Truncus arteriosus

Table 3. UCLA Congenital Heart Disease Functional Classification, Presence and Degree of Symptoms (from: Perloff 2008).

Class 1	Asymptomatic at all levels of activity
Class 2	Symptoms are present but do not curtail average, everyday activity
Class 3	Symptoms significantly curtail most but not all average, everyday activity
Class 4	Symptoms significantly curtail virtually all average, everyday activity and may be present at rest

was included in the present study.

Heart function was classified clinically, i.e. functional class does not necessarily correspond to severity of heart disease. A simple heart defect, for example, can be associated with poor heart function and a severe heart defect with good heart function [Stout 2005].

Data on status post intervention was collected for patients who delivered between 2009 and 2013. A variety of congenital heart defects demand surgical treatment, sometimes during the first months of life, either to repair the defect completely or to improve organ function and time of survival. Simple to moderate heart defects like atrial septal defects or ventricular septal defects can also be repaired by catheter intervention, reducing the burden for the patient in comparison with operational correction. Simple to moderate defects of the heart valves or the great arteries like pulmonary stenosis or aortic stenosis can also be treated catheter based by balloon dilatation via catheter. A more recent interventional alternative for operational valve replacement is the percutaneous pulmonary valve implantation, applied in previously operated heart defects like Truncus arteriosus or Tetralogy of Fallot [Eicken 2011]. It was recorded whether or not the patient had received surgical and interventional treatment, respectively, and if so, in which year the operation or catheter based intervention had been performed.

Data on blood oxygen level (SpO2) was collected for patients who delivered between 2009 and 2013. Blood oxygen level was measured in percentage, with levels less than or equal 95% defined as presence of cyanosis. Blood oxygen level as measured at the Outpatient Department for Adults with Congenital Heart Defects at the German Heart Centre Munich last before delivery was included in the present study.

Data on the presence and nature of an artificial heart valve was collected, differentiating homograft, i.e. a biological heart valve made of human tissue, heterograft, i.e. a biological heart valve made of animal tissue, and mechanical heart valve.

2-3.2 Obstetric data

The obstetric data that was collected in the present study includes data on gravidity and parity, status post Caesarean section, mode of delivery, indications for possible Caesarean sections, anesthesia used during delivery, start of delivery and indications for a possible induction of labor. Said data was collected for all patients with and without CHD.

Data on gravidity and parity was collected as part of the matching with patients without CHD (see 2-2).

Data on mode of delivery was collected, differentiating vaginal delivery, operative vaginal delivery and Caesarean section. Operative vaginal delivery was further differentiated in vacuum extraction and delivery by forceps. Caesarean section was further differentiated in primary Caesarean section, defined as a Caesarean section planned from the start, and secondary Caesarean section, defined as a Caesarean section which is decided upon while a vaginal delivery is already in progress, either following spontaneous onset of labor or following failed attempted vaginal delivery. In some international publications this is referred to as "emergency Caesarean section" [Cauldwell 2016, Ruys 2014b]. According to the definition of secondary Caesarean section mentioned above, however, emergency Caesarean section is an entity of its own in which Caesarean section has to be performed within 20 minutes in presence of an emergency that is life-threatening for the mother or the child or both, possibly but not necessarily to be subgrouped under secondary Caesarean section.

Additionally, data was collected on which mode of delivery was originally planned – a vaginal delivery or a primary Caesarean section, taking into account that both a planned vaginal delivery as well as a planned (primary) Caesarean section could later turn into a secondary Caesarean section due to obstetric problems and early onset of labor, respectively.

Data on indications for planned (primary) Caesarean sections and secondary Caesarean sections was collected, differentiating cardiac, obstetric and other indications. Cardiac indications were defined as poor heart function and worsening of heart function, respectively. Obstetric reasons were defined as fetal safety reasons, i.e. cardiotocography (CTG) based, fetal blood sampling (FBS) based, relative disproportion and malpresentation without failure to progress in labor. In the case of secondary Caesarean section, the definition was extended including failure to progress in labor. In case of failure to progress in second stage of labor, data was collected differentiating malpresentation, sufficient contractions with duration of more than two hours without progress in dilatation and insufficient contractions with duration of more than two hours without progress in dilatation. Other indications were defined as multiple unsuccessful induction of labor, requested by patient, status post Caesarean section, and a combination of both in the case of requested by patient in presence of status post Caesarean section. In the case of secondary Caesarean section, the definition was extended including planned (primary) Caesarean section in presence of early onset of labor.

It should be noted, however, that these differentiations can be somewhat vague in clinical practice, given the great number of combined indications. The indication for Caesarean section as stated in the patient file by the obstetrician in charge was decisive.

Data on anesthesia used during delivery was collected. In the case of vaginal delivery, data was collected differentiating epidural anesthesia, pudendal block, perineal infiltration and spinal anesthesia. In the case of Caesarean section, data was collected differentiating endotracheal anesthesia, epidural anesthesia, spinal anesthesia and the combination of epidural and spinal anesthesia.

Data was collected on whether delivery started spontaneously or following induction of labor.

Data on indications for induction of labor was collected differentiating medical reasons and logistical reasons. Medical reasons were further differentiated in pregnancy-induced maternal problems, fetal safety reasons and cardiac problems progressing. Pregnancy-induced maternal problems were defined as hypertension, edema, HELLP (Hemolysis, Elevated Liver enzymes, Low Platelet count) syndrome and maternal diabetes. Fetal safety reasons were defined as fetal growth restriction, early onset of labor, post-term pregnancy, polyhydramnios, status post abdominal version and CTG based. Logistical reasons were further differentiated in "because of long distance" between place of residence and the Frauenklinik, Klinikum rechts der Isar, Munich, and "not because of long distance".

2-3.3 Data regarding pregnancy outcome

The data regarding pregnancy outcome that was collected in the present study includes data on gestational age, maternal complications that occurred during delivery, and as data of the newborn APGAR score, umbilical cord pH and birth weight.

Gestational age was recorded in completed weeks of pregnancy, starting from the first day of the last menstruation, plus the number of days of the ongoing week. Derived from gestational age was presence of premature birth, defined as delivery before completion of 37 weeks of gestation.

Data on maternal complications during delivery was collected, differentiating obstetric complications and cardiovascular complications. Obstetric complications included postpartum hemorrhage and the so-called “4 Ts” regarding the pathology causing a possible postpartum hemorrhage, namely tissue, thrombin, tears and tonus, each of which could also occur on its own, i.e. without resulting in postpartum hemorrhage. Tears were further differentiated in uncomplicated tear, complicated tear, episiotomy for maternal reason and episiotomy for fetal reason. In the case of postpartum hemorrhage, hemoglobin (Hb) values before and after hemorrhage as well as data on how much red cell concentrate (RCC) and fresh frozen plasma (FFP) was transfused was collected. Cardiovascular complications included acute heart failure, acute coronary syndrome, ventricular tachycardia or fibrillation, severe bradycardia and embolism.

Data on APGAR score was collected three times, namely one, five and ten minutes after birth. The APGAR score is used to evaluate the health of the newborn. Zero to two points are given in the categories appearance (A), pulse (P), grimace (G), activity (A) and respiration (R), resulting in a maximum score of ten points, with scores above six regarded as normal, scores from four to six regarded as fairly low, and scores below four regarded as critically low.

Data on umbilical cord pH was collected, based on blood gas analysis following puncture of an umbilical artery. Values below 7.10 are regarded as presence of acidosis.

Data on birth weight was collected, recorded directly after birth in grams. Applying percentile curves, it was inferred from the combination of birth weight and gestational age whether or not the newborn was small for gestational age (SGA).

2-4 Statistical analysis

Data analysis was performed using SPSS software version 22.0 (SPSS Inc., IBM).

Chi square tests were used for comparing differences in categorical data between independent patient groups.

Fisher's exact tests were applied if any expected cell count was below 5.

Student t tests were used for comparing differences in continuous data between independent patient groups.

According to convention, P values below 0.05 were considered statistically significant.

3. Results

3-1 Characteristics of the study population

Maternal baseline characteristics in women with CHD are outlined in Table 4.

Maternal age ranged from 20 to 40 years of age at delivery. Parity ranged from zero to two prior deliveries. Since maternal age and parity were among the matching parameters, mean maternal age and percentage of nulliparous and multiparous were the same in women without CHD.

Table 4. Maternal baseline characteristics in women with CHD.

		n = 116
		n (%)
Age (years) (SD)		29.7 (±4.5)
Parity		
	Nulliparous	85 (73.3)
	Multiparous	31 (26.7)
Status post Caesarean section		
	Prior Caesarean section	11 (9.5)
	No prior Caesarean section	105 (90.5)
Severity of CHD (according to the ACC)		
	Simple	30 (25.9)
	Moderate	59 (50.9)
	Severe	27 (23.2)
Functional class (according to Perloff)		
	Class 1	47 (40.5)
	Class 2	66 (56.9)
	Class 3	3 (2.6)
	Class 4	0 (0.0)

Diagnosis		
	Post-tricuspid shunts:	9 (7.8)
	VSD	
	Pre-tricuspid shunts:	17 (14.7)
	ASD, PFO	
	Left heart obstructions:	17 (14.7)
	AS, BAV, CoA, SAS	
	Right heart obstructions:	33 (28.4)
	DORV, PS, TOF	
	Complex anomalies:	24 (20.7)
	ccTGA, TGA, TOF/APV, TrA	
	Hereditary:	7 (6.0)
	Marfan's syndrome	
	Congenital rhythm anomalies:	2 (1.7)
	atrioventricular block	
	Other:	7 (6.0)
	aortic aneurysm, Ebstein's anomaly, congenital form of HOCM, MVP	

AS = aortic stenosis, ASD = atrial septal defect, BAV = bicuspid aortic valve, ccTGA = congenitally corrected transposition of the great arteries, CoA = coarctation of the aorta, DORV = double outlet right ventricle, HOCM = hypertrophic obstructive cardiomyopathy, MVP = mitral valve prolapse, PFO = patent foramen ovale, PS = pulmonary stenosis, SAS = subaortic stenosis, TGA = transposition of the great arteries, TOF = tetralogy of Fallot, TOF/APV = tetralogy of Fallot with absent pulmonary valve, TrA = truncus arteriosus, VSD = ventricular septal defect

Classification showed that severity of CHD and functional class did not correspond. With regard to severity, approximately half of the cases were considered moderate, with approximately a quarter of cases being considered simple and severe each. With regard to the clinical cardiac status, 97.4% of cases belonged to functional classes 1 and 2 (with the bigger share in functional class 2), and only 2.6% to functional class 3, with no cases in a possible functional class 4. Distribution to functional classes was similar in patients with simple and moderate heart defects. There were significantly less patients with severe heart defects in functional class 1 (*P* = 0.029, see Table 5).

Table 5. Heart function according to severity of heart defect.

		Severity of CHD			
		Simple	**Moderate**	**Severe**	
		n = 30	**n = 59**	**n = 27**	
		n (%)	**n (%)**	**n (%)**	***P***
Functional class	Class 1	14 (46.7)	28 (47.5)	5 (18.5)	0.029
	Class 2	16 (53.3)	30 (50.8)	20 (74.1)	0.117
	Class 3	0 (0.0)	1 (1.7)	2 (7.4)	0.197

Analysis of the statistical relation between group of CHD and severity of CHD showed significant differences for all severity grades (*P* < 0.001). Post-tricuspid shunts were more likely to be simple than pre-tricuspid shunts. Apart from complex anomalies, the only group of heart defects being regarded as severe were right heart obstructions (see Table 6).

Analysis of the statistical relation between group of CHD and heart function showed that shunt lesions and congenital rhythm anomalies were the only heart defects with a bigger share in functional class 1, with all other heart defects having their bigger share in functional class 2 (see Table 6).

Table 6. Severity of CHD and heart function according to group of CHD.

		Group of CHD								
		Post-tricuspid shunts	**Pre-tricuspid shunts**	**Left heart obstructions**	**Right heart obstructions**	**Complex anomalies**	**Marfan's syndrome**	**Congenital rhythm anomalies**	**Other**	
		n = 9	**n = 17**	**n = 17**	**n = 33**	**n = 24**	**n = 7**	**n = 2**	**n = 7**	
		n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	***P***
Severity of CHD	Simple	7 (77.8)	7 (41.2)	4 (23.5)	9 (27.3)	0 (0.0)	0 (0.0)	2 (100.0)	1 (14.3)	< 0.001
	Moderate	2 (22.2)	10 (58.8)	13 (76.5)	21 (63.6)	0 (0.0)	7 (100.0)	0 (0.0)	6 (85.7)	< 0.001
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	3 (9.1)	24 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	< 0.001
Functional class	Class 1	6 (66.7)	10 (58.8)	8 (47.1)	10 (30.3)	5 (20.8)	3 (42.9)	2 (100.0)	3 (42.9)	0.053
	Class 2	3 (33.3)	7 (41.2)	9 (52.9)	22 (66.7)	17 (70.8)	4 (57.1)	0 (0.0)	4 (57.1)	0.213
	Class 3	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.806

Maternal risk factors for complications during and outcome of pregnancy are outlined in Table 7.

Table 7. Maternal risk factors.

		with CHD	without CHD	
		n = 116	**n = 348**	
		n (%)	**n (%)**	***P***
Body mass index (SD)		23,20 (±3,95)	22,76 (±3,86)	0.298
	≤17.5	0 (0.0)	9 (2.6)	0.120
	≥30.0	8 (6.9)	17 (4.9)	0.406
Smoking		1 (0.9)	6 (1.7)	0.686
Preeclampsia		1 (0.9)	11 (3.2)	0.310
Diabetes		2 (1.7)	23 (6.6)	0.044
	Preexisting	0 (0.0)	3 (0.9)	0.577
	Gestational	2 (1.7)	20 (5.7)	0.077
Prior Caesarean section		11 (9.5)	17 (4.9)	0.072

Body mass index (BMI) was slightly higher in women with CHD. Smoking, preeclampsia and diabetes were more common in women without CHD, with a significant difference for diabetes only (*P* = 0.044). A total of 9.5% of patients with prior Caesarean section in women with CHD compared with 4.9% in women without CHD (*P* = 0.072).

Additional cardiologic data collected on the 73 patients with CHD who delivered between 2009 and 2013 at the Frauenklinik, Klinikum rechts der Isar, Munich, is outlined in Table 8.
69.8% of patients had received intervention in form of either surgical or interventional treatment for their underlying heart defect.
There was one patient with a blood oxygen level of 94%.

Table 8. Additional cardiologic data 2009-2013.

		n = 73
		n (%)
Status post intervention		51 (69.8)
	Surgical treatment	45 (61.6)
	Interventional treatment	6 (8.2)
Cyanosis		1 (1.4)
Fontan circulation		1 (1.4)
Right system ventricle		13 (17.8)
Pacer		1 (1.4)
ICD		2 (2.7)
Artificial heart valve		6 (8.2)
	Homograft	2 (2.7)
	Heterograft	3 (4.1)
	Mechanical heart valve	1 (1.4)

3-2 Mode of delivery

Details pertaining to mode of delivery are shown in Table 9.

The rate of Caesarean section was significantly higher in women with CHD. Caesarean section was performed in 46.6% of pregnancies in women with CHD, compared with 33.6% of pregnancies in women without CHD (P = 0.012). The rate of primary Caesarean section and the rate of secondary Caesarean section were both higher in women with CHD.

The rate of spontaneous vaginal delivery (44.8% vs. 56.0%, P = 0.036) as well as the rate of operative vaginal delivery (8.6% vs. 10.4%, P = 0.590) was lower in women with CHD.

Table 9. Mode of delivery.

			with CHD	without CHD	
			n = 116	n = 348	
			n (%)	n (%)	*P*
Vaginal delivery			62 (53.4)	231 (66.4)	0.012
	Spontaneous		52 (44.8)	195 (56.0)	0.036
	Operative vaginal		10 (8.6)	36 (10.4)	0.590
		Vacuum extraction	10 (8.6)	33 (9.5)	0.782
		Forceps	0 (0.0)	3 (0.9)	0.577
Caesarean section			54 (46.6)	117 (33.6)	0.012
	Primary		24 (20.7)	51 (14.7)	0.126
	Secondary		30 (25.9)	66 (18.9)	0.112

In patients with and without CHD, mode of delivery was compared according to parity (see Tables 10a and 10b).

In women with and without CHD, vaginal delivery rate was higher in multiparous patients. The difference was significant in women without CHD only ($P = 0.002$). Whereas primary Caesarean section rate was actually higher in multiparous patients with CHD ($P = 0.761$), it was significantly lower in multiparous patients without CHD ($P = 0.009$).

Table 10a. Mode of delivery according to parity in patients with CHD.

		Nulliparous	Multiparous	
		n = 85	**n = 31**	
		n (%)	**n (%)**	***P***
Vaginal delivery		43 (50.6)	19 (61.3)	0.307
Caesarean section		42 (49.4)	12 (38.7)	0.307
	Primary	17 (20.0)	7 (22.6)	0.761
	Secondary	25 (29.4)	5 (16.1)	0.148

Table 10b. Mode of delivery according to parity in women without CHD.

		Nulliparous	Multiparous	
		n = 255	**n = 93**	
		n (%)	**n (%)**	***P***
Vaginal delivery		157 (61.6)	74 (79.6)	0.002
Caesarean section		98 (38.4)	19 (20.4)	0.002
	Primary	45 (17.6)	6 (6.5)	0.009
	Secondary	54 (20.8)	13 (14.0)	0.152

Mode of delivery was compared in all multiparous patients according to status post Caesarean section (see Tables 11a and 11b). In both women with and without CHD, Caesarean section rate was significantly higher in multiparous patients with prior Caesarean section compared with multiparous patients without prior Caesarean section (81.8% vs. 15.0% in women with CHD, $P < 0.001$, and 58.8% vs. 11.8% in women without CHD, $P < 0.001$, respectively).

Table 11a. Mode of delivery according to status post Caesarean section in women with CHD.

		Prior Caesarean section	No prior Caesarean section	
		n = 11*	n = 20*	
		n (%)	n (%)	*P*
Vaginal delivery		2 (18.2)	17 (85.0)	< 0.001
Caesarean section		9 (81.8)	3 (15.0)	< 0.001
	Primary	4 (36.4)	3 (15.0)	0.210
	Secondary	5 (45.5)	0 (0.0)	0.003

Table 11b. Mode of delivery according to status post Caesarean section in women without CHD.

		Prior Caesarean section	No prior Caesarean section	
		n = 17*	n = 76*	
		n (%)	n (%)	*P*
Vaginal delivery		7 (41.2)	67 (88.2)	< 0.001
Caesarean section		10 (58.8)	9 (11.8)	< 0.001
	Primary	4 (23.5)	2 (2.6)	0.010
	Secondary	6 (35.3)	7 (9.2)	0.012

*Only patients with a possible prior Caesarean section, i.e. multiparous patients (n = 31 in patients with CHD and n = 93 in patients without CHD, respectively), were included.

However, the difference in rate of Caesarean section after prior Caesarean section between women with and without CHD was not significant (*P* = 0.249, see Table 12).

Table 12. Mode of delivery in women with prior Caesarean section.

		with CHD	without CHD	
		n = 11	n = 17	
		n (%)	n (%)	*P*
Vaginal delivery		2 (18.2)	7 (41.2)	0.249
Caesarean section		9 (81.8)	10 (58.8)	0.249
	Primary	4 (36.4)	4 (23.5)	0.671
	Secondary	5 (45.5)	6 (35.3)	0.701

In women with CHD, mode of delivery was compared according to division in groups for severity of CHD, functional class, group of CHD and subtype of left heart obstruction (see Tables 13a, 13b, 14a and 14b).

Table 13a. Mode of delivery according to severity of CHD.

		Severity of CHD			
		Simple	Moderate	Severe	
		n = 30	n = 59	n = 27	
		n (%)	n (%)	n (%)	*P*
Vaginal delivery		15 (50.0)	35 (59.3)	12 (44.4)	0.398
Caesarean section		15 (50.0)	24 (40.7)	15 (55.6)	0.398
	Primary	3 (10.0)	11 (18.7)	10 (37.1)	0.036
	Secondary	12 (40.0)	13 (22.0)	5 (18.5)	0.114

There was no correlation between severity of CHD and mode of delivery in general (P = 0.398). However, detailed analysis showed that the rate of primary Caesarean sections increases significantly with severity (P = 0.036).

Table 13b. Mode of delivery according to heart function.

		Functional class			
		Class 1	**Class 2**	**Class 3**	
		n = 47	**n = 66**	**n = 3**	
		n (%)	**n (%)**	**n (%)**	***P***
Vaginal delivery		30 (63.8)	31 (47.0)	1 (33.3)	0.146
Caesarean section		17 (36.2)	35 (53.0)	2 (66.7)	0.146
	Primary	8 (17.0)	16 (24.2)	0 (0.0)	0.600
	Secondary	9 (19.2)	19 (28.8)	2 (66.7)	0.111

In the case of functional classes, the ratio of vaginal delivery and Caesarean section tended to invert according to worsening of the clinical cardiac status (P = 0.146).

With regard to group of CHD, rates of vaginal delivery over 70% could be observed in pre-tricuspid shunts, congenital rhythm anomalies and heart defects classified as other (P = 0.255, see Tables 1 and 4 for details). As for Caesarean sections, Marfan's syndrome stood out with 71.4% of Caesarean sections, more than half of them primary Caesarean sections.

Table 14a. Mode of delivery according to group of CHD.

		Group of CHD								
		Post-tricuspid shunts	**Pre-tricuspid shunts**	**Left heart obstructions**	**Right heart obstructions**	**Complex anomalies**	**Marfan's syndrome**	**Congenital rhythm anomalies**	**Other**	
		n = 9	**n = 17**	**n = 17**	**n = 33**	**n = 24**	**n = 7**	**n = 2**	**n = 7**	
		n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	***P***
Vaginal delivery		4 (44.4)	13 (76.5)	8 (47.1)	17 (51.5)	11 (45.8)	2 (28.6)	2 (100.0)	5 (71.4)	0.255
Caesarean section		5 (55.6)	4 (23.5)	9 (52.9)	16 (48.5)	13 (54.2)	5 (71.4)	0 (0.0)	2 (28.6)	0.255
	Primary	1 (11.1)	0 (0.0)	4 (23.5)	7 (21.2)	8 (33.3)	3 (42.9)	0 (0.0)	1 (14.3)	0.123
	Secondary	4 (44.4)	4 (23.5)	5 (29.4)	9 (27.3)	5 (20.8)	2 (28.6)	0 (0.0)	1 (14.3)	0.902

For subtypes of left heart obstruction, no significant difference in mode of delivery could be observed.

Table 14b. Mode of delivery according to subtype of left heart obstruction.

		Subtype of left heart obstruction				
		AS	**BAV**	**CoA**	**SAS**	
		n = 5	**n = 2**	**n = 9**	**n = 1**	
		n (%)	**n (%)**	**n (%)**	**n (%)**	***P***
Vaginal		1 (20.0)	1 (50.0)	5 (55.6)	1 (100.0)	0.620
Caesarean section		4 (80.0)	1 (50.0)	4 (44.4)	0 (0.0)	0.620
	Primary	2 (40.0)	0 (0.0)	2 (22.2)	0 (0.0)	0.824
	Secondary	2 (40.0)	1 (50.0)	2 (22.2)	0 (50.0)	0.729

AS = aortic stenosis, BAV = bicuspid aortic valve, CoA = coarctation of the aorta, SAS = subaortic stenosis

Indications for primary and secondary Caesarean sections were examined individually (see Tables 15a and 15b).

Table 15a. Indications for primary Caesarean sections.

		with CHD	without CHD	
		n = 24	**n = 51**	
		n (%)	**n (%)**	***P***
Cardiac reason		8 (33.3)	–	< 0.001
Obstetric reason		9 (37.5)	43 (84.3)	< 0.001
Other		7 (29.2)	8 (15.7)	0.219
	Maternal request	4 (16.7)	5 (9.8)	0.455

Cardiac reasons came to 33.3% of primary Caesarean sections in women with CHD. Obstetric reasons for primary Caesarean sections were significantly higher in women without CHD ($P < 0.001$). There was no significant difference in reasons classified as “other” for primary

Caesarean sections in women with and without CHD (P = 0.219). In both cases, Caesarean section on maternal request predominated with a relative percentage of 57.1% (n = 4 out of 7) and 62.5% (n = 5 out of 8), respectively.

Table 15b. Indications for secondary Caesarean sections.

	with CHD	**without CHD**	
	n = 30	**n = 66**	
	n (%)	**n (%)**	***P***
Cardiac reason	2 (6.7)	–	0.095
Obstetric reason	27 (90.0)	62 (93.9)	0.674
Other	1 (3.3)	4 (6.1)	1.000

In contrast to primary Caesarean sections, there was no significant difference in indications for secondary Caesarean sections in women with and without CHD. Cardiac reasons came to no more than 6.7% of secondary Caesarean sections in women with CHD. In women with and without CHD, obstetric reasons predominated clearly (90.0% vs. 93.9%).

Details pertaining to anesthesia used in vaginal delivery and Caesarean section, respectively, are shown in Tables 16a and 16b.

With regard to anesthesia used in vaginal delivery, there was a significantly higher rate of epidural anesthesia in women with CHD (P = 0.002) as well as a significantly higher rate of perineal infiltration in women without CHD (P < 0.001).

There were no significant differences with regard to anesthesia used in Caesarean section in women with and without CHD.

Table 16a. Anesthesia used in vaginal delivery.

	with CHD	without CHD	
	n = 31*	n = 122*	
	n (%)	n (%)	*P*
Epidural anesthesia	28 (90.3)	74 (60.7)	0.002
Pudendal block	1 (3.2)	1 (0.8)	0.365
Perineal infiltration	1 (3.2)	45 (36.9)	<0.001
Spinal anesthesia	1 (3.2)	2 (1.6)	0.496

*Anesthesia was used in 31 of 62 vaginal deliveries in women with CHD, and in 122 of 231 vaginal deliveries in women without CHD, respectively (50.0% vs. 52.8%, $P = 0.694$).

Table 16b. Anesthesia used in Caesarean section.

	with CHD	without CHD	
	n = 54*	n = 117*	
	n (%)	n (%)	*P*
Endotracheal anesthesia	9 (16.7)	15 (12.8)	0.501
Epidural anesthesia	16 (29.6)	30 (25.6)	0.585
Spinal anesthesia	28 (51.9)	69 (59.0)	0.382
Combination of epidural and spinal anesthesia	1 (1.9)	3 (2.6)	1.000

*Total number of cases of Caesarean sections in women with and without CHD

3-3 Induction of labor

Excluding primary Caesarean sections (20.7% vs. 14.7%), vaginal delivery was attempted in 79.3% of pregnancies in women with CHD and 85.3% of pregnancies in women without CHD.

Details pertaining to induction of labor are shown in Table 17.

Induction of labor was performed in 45.7% of attempted vaginal deliveries in women with CHD, compared with 27.9% in women without CHD ($P = 0.001$).

Table 17. Induction of labor.

			with CHD	**without CHD**	
			n = 92*	**n = 297***	
			n (%)	**n (%)**	***P***
Induction of labor			42 (45.7)	83 (27.9)	0.001
Indication for induction of labor					
	Medical reason		27 (64.3)	82 (98.8)	< 0.001
	Logistical reason		15 (35.7)	1 (1.2)	< 0.001
		“because of long distance”	13 (31.0)	0 (0.0)	< 0.001

*To avoid falsification of results due to different rates of primary Caesarean sections in women with and without CHD (20.7% vs. 14.7%), only cases of attempted vaginal delivery (n = 389) were examined. 24 and 51 primary Caesarean sections, respectively, were excluded.

As can be seen in Tables 18a and 18b, performance of induction of labor was associated with higher rates of secondary Caesarean section in both women with and without CHD. In women with CHD, secondary Caesarean section rate was 24.0% without induction of labor and 42.9% following induction ($P = 0.055$). In women without CHD, secondary Caesarean section rate was 17.8% without induction of labor and 33.7% following induction ($P = 0.003$).

Table 18a. Mode of delivery according to performance of induction of labor in women with CHD.

	Induction performed	Induction not performed	
	n = 42*	n = 50*	
	n (%)	n (%)	*P*
Vaginal delivery	24 (57.1)	38 (76.0)	0.055
Secondary Caesarean section	18 (42.9)	12 (24.0)	0.055

Table 18b. Mode of delivery according to performance of induction of labor in women without CHD.

	Induction performed	Induction not performed	
	n = 83*	n = 214*	
	n (%)	n (%)	*P*
Vaginal delivery	55 (66.3)	176 (82.2)	0.003
Secondary Caesarean section	28 (33.7)	38 (17.8)	0.003

*As in Table 17, only cases of attempted vaginal delivery (n = 92 in patients with CHD and n = 297 in patients without CHD, respectively) were examined.

Indications for induction of labor differed with high significance in women with and without CHD. In women without CHD, 98.8% of inductions of labor were performed for medical reasons, compared with only 64.3% in women with CHD (P < 0.001). Of the remaining 35.7% of inductions of labor which were performed for logistical reasons in women with CHD, a clear majority was performed “because of long distance“ between the patient’s place of residence and the Frauenklinik, Klinikum rechts der Isar, Munich, the relative percentage being 86.7% (n = 13 out of 15).

In women with CHD, mode of delivery following induction of labor was compared according to the different severity grades and functional classes, respectively (see Tables 19a and 19b). As for severity of CHD, there was no correlation between mode of delivery following induction of labor (P = 0.843). In the case of functional classes, the ratio of vaginal delivery and secondary Caesarean sections tended to invert according to worsening of heart function (P = 0.254).

Table 19a. Mode of delivery following induction of labor according to severity of CHD.

	Severity of CHD			
	Simple	**Moderate**	**Severe**	
	n = 14*	**n = 21***	**n = 7***	
	n (%)	**n (%)**	**n (%)**	***P***
Vaginal delivery	7 (50.0)	13 (61.9)	4 (57.1)	0.843
Secondary Caesarean section	7 (50.0)	8 (38.1)	3 (42.9)	0.843

*Total number of induced patients in each category

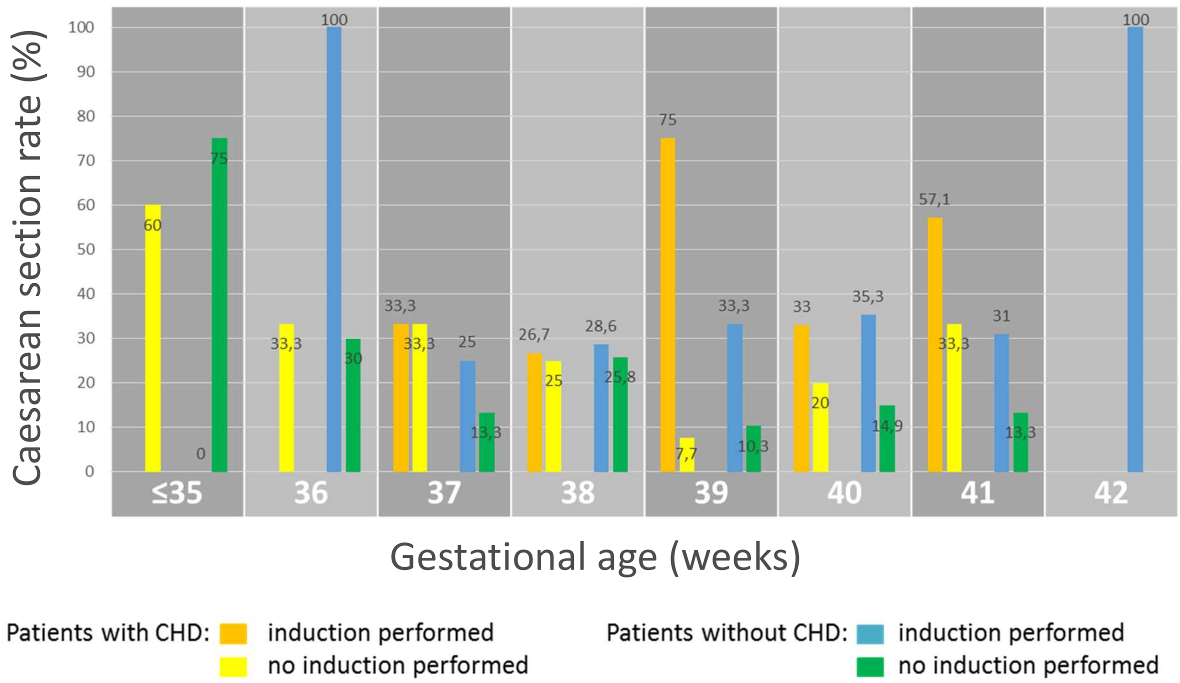
Table 19b. Mode of delivery following induction of labor according to heart function in women with CHD.

	Functional class			
	Class 1	**Class 2**	**Class 3**	
	n = 19*	**n = 21***	**n = 2***	
	n (%)	**n (%)**	**n (%)**	***P***
Vaginal delivery	12 (63.2)	12 (57.1)	0 (0.0)	0.254
Secondary Caesarean section	7 (36.8)	9 (42.9)	2 (100.0)	0.254

*Total number of induced patients in each category

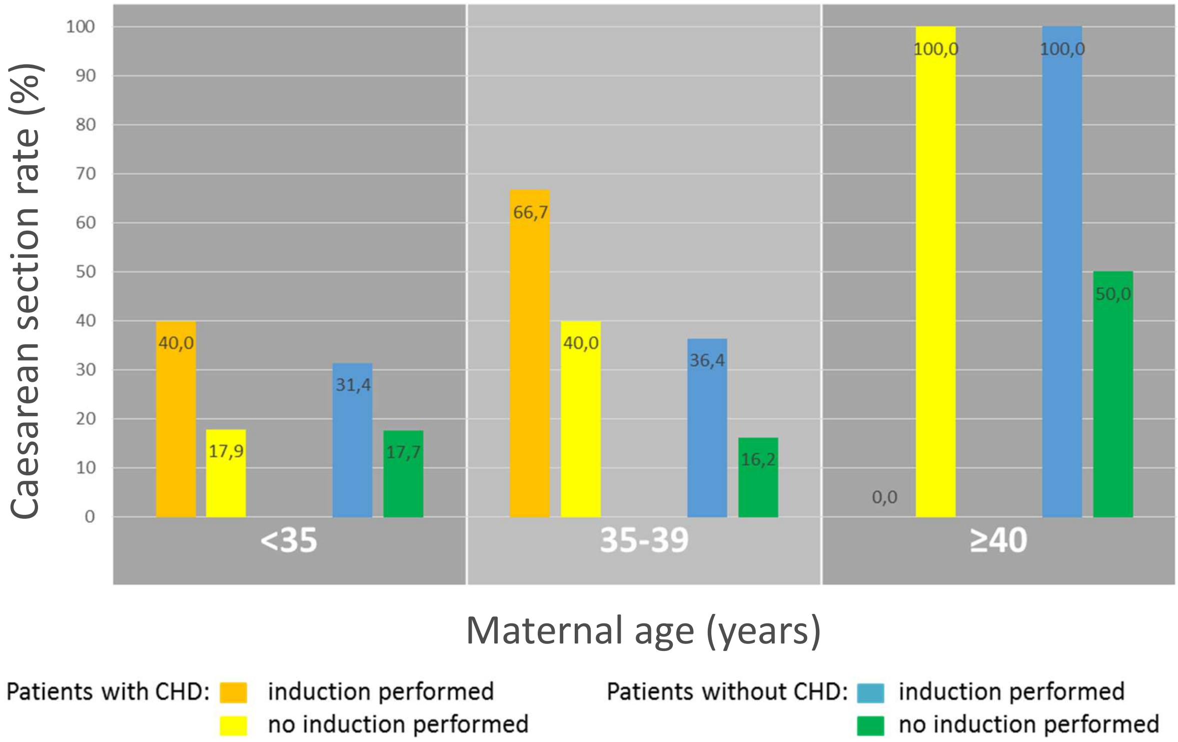
Secondary Caesarean section rate was further analyzed according to performance of induction of labor in combination with gestational age, maternal age and parity (see Figures 3a, 3b and 3c).

Figure 3a. Secondary Caesarean rate according to performance of induction of labor in combination with gestational age.



With regard to gestational age, the rate of secondary Caesarean section following induction of labor was higher than the rate of secondary Caesarean section without performance of induction of labor from gestational week 36 onwards in patients without CHD, and from gestational week 38 onwards in women with CHD. However, in both women with and without CHD, a significantly higher rate of Caesarean section following induction of labor could be observed for gestational week 39 only (75% vs. 7.7% in women with CHD, P = 0.003, and 33.3% vs. 10.3% in women without CHD, P = 0.036).

Figure 3b. Secondary Caesarean section rate according to performance of induction of labor in combination with maternal age.

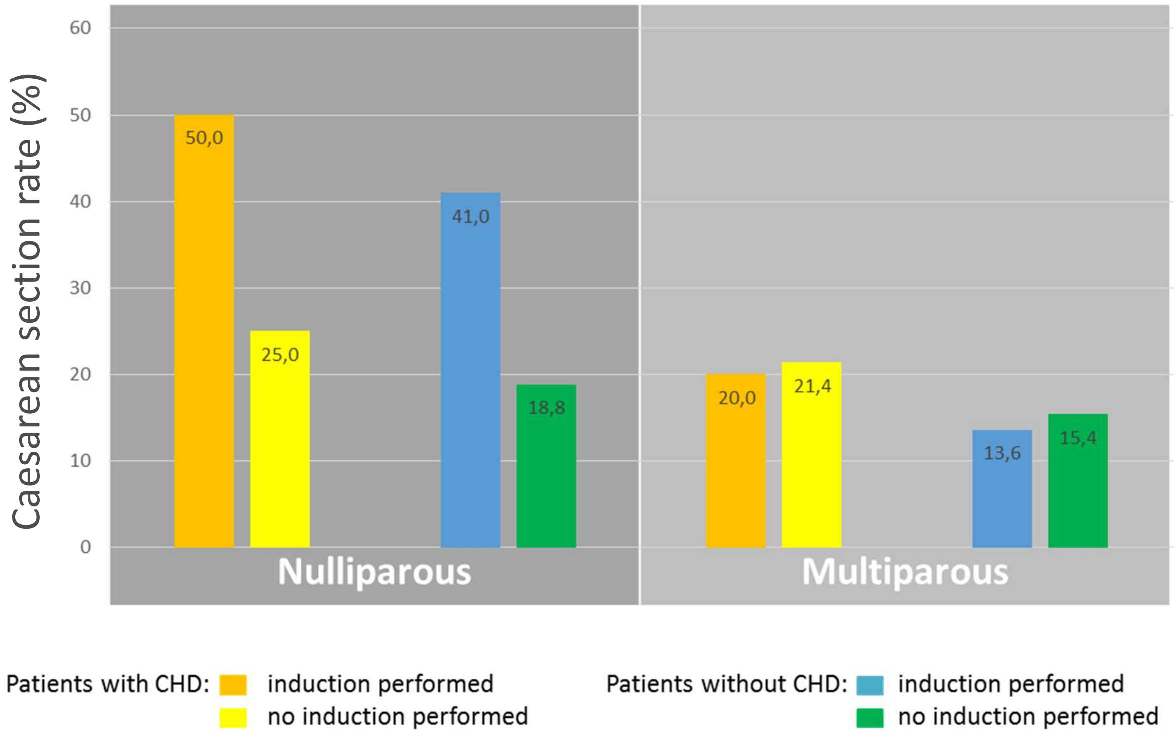


With regard to maternal age, in both women with and without CHD, the rate of secondary Caesarean section following induction of labor was significantly higher than the rate of secondary Caesarean section without performance of induction of labor in patients below 35 years of age (40% vs. 17.9% in women with CHD, $P = 0.036$, and 31.4% vs. 17.7% in women without CHD, $P = 0.019$).

With regard to parity, in both women with and without CHD, rate of secondary Caesarean section was significantly higher following induction of labor in nulliparous patients (50% vs. 25% in women with CHD, $P = 0.033$, and 41% vs. 18.8% in women without CHD, $P = 0.001$). Furthermore, in both women with and without CHD, rate of secondary Caesarean section was actually lower following induction of labor in multiparous patients (20% vs.

21.4% in women with CHD, P = 1.000, and 13.6% vs. 15.4% in women without CHD, P = 1.000)

Figure 3c. Secondary Caesarean section rate according to performance of induction of labor in combination with parity.



3-4 Pregnancy outcome

Pregnancy outcome is outlined in Table 20.

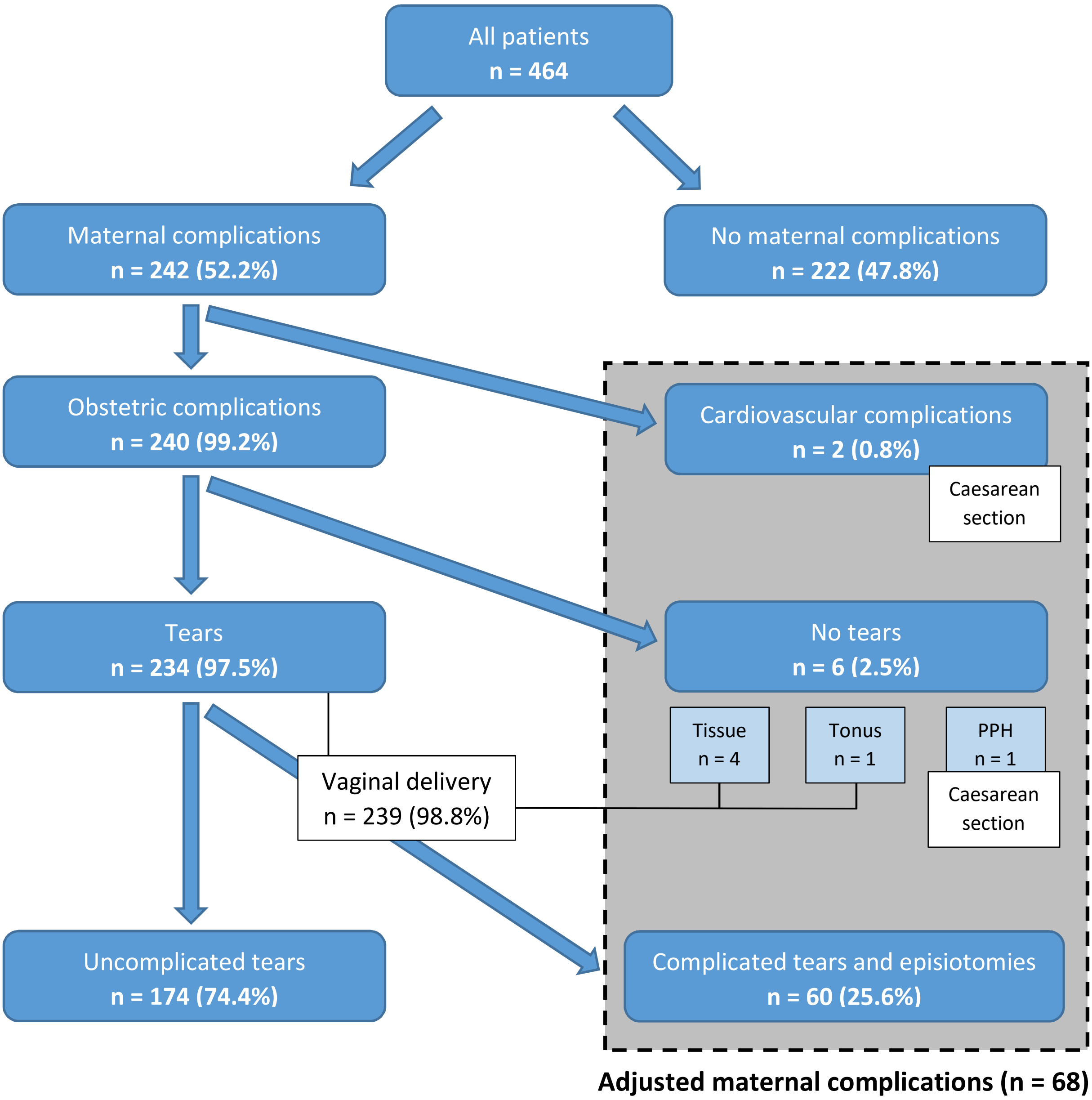
There were no cases of maternal, perinatal or neonatal mortality, and no cases of adverse neonatal outcome in the present study. Overall, mean pregnancy duration and the rate of premature birth were similar in women with and without CHD. Lower mean birth weight (P = 0.004) and small for gestational age (P < 0.001) were significantly more common in women with CHD.

As shown in Figure 4, maternal complications occurred in 52.2% of all deliveries (n = 242 out of 464). There were no cases of acute heart failure, acute coronary syndrome, ventricular tachycardia or fibrillation in the present study. Almost all of the maternal complications were obstetric complications (n = 240 out of 242, relative percentage 99.2%), which occurred in 38.8% of deliveries in women with CHD in comparison with 56.0% of deliveries in women without CHD (*P* = 0.001). The vast majority of obstetric complications being tears (n = 234 out of 240, relative percentage 97.5%), almost all of the maternal complications happened to have occurred in vaginal deliveries (n = 239 out of 242, relative percentage 98.8%). Uncomplicated tears made up for 74.4% of all tears (n = 174 out of 234).

Table 20. Pregnancy outcome.

	with CHD	**without CHD**	
	n = 116	**n = 348**	
	n (%)	**n (%)**	***P***
Pregnancy duration (weeks) (SD)	38.7 (±2.3)	38.7 (±2.0)	0.054
Premature birth	13 (11.2)	32 (9.2)	0.526
Birth weight (g) (SD)	3092 (±588)	3267 (±547)	0.004
SGA	19 (16.4)	8 (2.3)	< 0.001
APGAR score (after 1 / 5 / 10 min)	8.32 / 9.21 / 9.65	8.25 / 9.18 / 9.65	
Arterial cord pH (SD)	7.28 (±0.08)	7.26 (±0.09)	0.017
Obstetric complications	45 (38.8)	195 (56.0)	0.001
Adjusted maternal complications (excluding uncomplicated tears)	12 (10.3)	56 (16.1)	0.130
Postpartum hemorrhage	1 (0.9)	0 (0.0)	0.250

Figure 4. Maternal complications.



Single case analysis showed that the three cases of maternal complications that occurred in Caesarean sections were (a) the only two cases of maternal complications that were not obstetric but cardiovascular, as well as (b) the only case of adverse maternal outcome found in the present study in the form of postpartum hemorrhage.

With regard to the two cases of cardiovascular complications, one patient with Marfan's syndrome, delivering by primary Caesarean section under endotracheal anesthesia, showed a drop in heart rate to below 40 beats per minute and had to be monitored in the cardiologic intensive care unit after delivery. Another patient with Marfan's syndrome, delivering by secondary Caesarean section under spinal anesthesia, suffered from fever sub partu, persistence of fever after delivery, a small pulmonary embolism and a post-operative seroma. As recorded last before delivery, the patient showed an SpO2 of 94%. Secondary Caesarean section in this patient was indicated due to a suspicious CTG and suspicion of amniotic infection syndrome. The newborn showed an APGAR score of 6, 7 and 8, and was monitored in the neonatal intensive care unit.

With regard to the one case of postpartum hemorrhage, the patient in question was one of the two high-risk patients who delivered by planned Caesarean section under epidural anesthesia directly in the German Heart Centre Munich. With an underlying heart disease of ccTGA, the patient showed presence of mechanical heart valve. Hemoglobin value dropped from 12 before hemorrhage to 6 after hemorrhage. The patient was given 1200 ml of RCC and 4000 ml of FFP. In the second patient who delivered directly at the German Heart Centre Munich, showing a high-grade aortic stenosis, no complications occurred.

Excluding uncomplicated tears from maternal complications, adjusted maternal complications occurred in 14.7% of deliveries (n = 68 out of 464), with more complications in women without CHD (16.1% vs. 10.3%, $P = 0.130$).

Complicated tears and episiotomies made up 88.2% of adjusted maternal complications (n = 60 out of 68). In women with CHD, 41.7% (n = 5 out of 12) of adjusted complications were neither complicated tears nor episiotomies, but cardiovascular complications (n = 2), tissue (n = 1), tonus (n = 1) and postpartum hemorrhage (n = 1), whereas in women without CHD, it were no more than 5.4% (n = 3 out of 56), with three cases of tissue complications.

For CHD patients only, rate of adjusted maternal complications was analyzed according to severity of CHD, heart function and group of CHD (see Tables 21a, 21b and 21c).

For all patients, rate of adjusted maternal complications was analyzed according to parity and anesthesia used in vaginal delivery (see Tables 22a, 22b, 23a and 23b).

Table 21a. Maternal complications according to severity of CHD.

	Severity of CHD			
	Simple	**Moderate**	**Severe**	
	n = 30	**n = 59**	**n = 27**	
	n (%)	**n (%)**	**n (%)**	***P***
Maternal complications	2 (6.7)	7 (11.9)	3 (11.1)	0.852
No maternal complications or uncomplicated tear	28 (93.3)	52 (88.1)	24 (88.9)	0.852

Table 21b. Maternal complications according to heart function in women with CHD.

	Functional class			
	Class 1	**Class 2**	**Class 3**	
	n = 47	**n = 66**	**n = 3**	
	n (%)	**n (%)**	**n (%)**	***P***
Maternal complications	4 (8.5)	8 (12.1)	0 (0.0)	0.826
No maternal complications or uncomplicated tear	43 (91.5)	58 (87.9)	3 (100.0)	0.826

Table 21c. Maternal complications according to group of CHD.

	Group of CHD								
	Post-tricuspid shunts	**Pre-tricuspid shunts**	**Left heart obstructions**	**Right heart obstructions**	**Complex anomalies**	**Marfan's syndrome**	**Congenital rhythm anomalies**	**Other**	
	n = 9	**n = 17**	**n = 17**	**n = 33**	**n = 24**	**n = 7**	**n = 2**	**n = 7**	
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	***P***
Maternal complications	0 (0.0)	2 (11.8)	3 (17.6)	2 (6.1)	2 (8.3)	2 (28.6)	0 (0.0)	1 (14.3)	0.510
No maternal complications or uncomplicated tear	9 (100.0)	15 (88.2)	14 (82.4)	31 (93.9)	22 (91.7)	5 (71.4)	2 (100.0)	6 (85.7)	0.510

There was no significant difference in rate of adjusted maternal complications with regard to severity of CHD, heart function and group of CHD.

With regard to parity, rate of adjusted maternal complications differed in women with and without CHD. In women with CHD, there were more complications in multiparous women (16.1% vs. 8.2%, $P = 0.299$), whereas in women without CHD, rate of adjusted maternal complications was significantly higher in nulliparous women (21.2% vs. 2.2%, $P < 0.001$).

Table 22a. Maternal complications according to parity in women with CHD.

	Nulliparous	Multiparous	
	n = 85	n = 31	
	n (%)	n (%)	*P*
Maternal complications	7 (8.2)	5 (16.1)	0.299
No maternal complications or uncomplicated tear	78 (91.8)	26 (83.9)	0.299

Table 22b. Maternal complications according to parity in women without CHD.

	Nulliparous	Multiparous	
	n = 255	n = 93	
	n (%)	n (%)	*P*
Maternal complications	54 (21.2)	2 (2.2)	< 0.001
No maternal complications or uncomplicated tear	201 (78.8)	91 (97.8)	< 0.001

There was no significant difference in rate of adjusted maternal complications with regard to anesthesia used in vaginal delivery. The three cases of maternal complications in Caesarean section occurred under endotracheal, epidural and spinal anesthesia, respectively ($P = 0.422$).

Table 23a. Maternal complications according to anesthesia used in vaginal delivery in women with CHD.

	Anesthesia used in vaginal delivery				
	Epidural anesthesia	**Perineal infiltration**	**Pudendal block**	**Spinal anesthesia**	
	n = 28*	**n = 1***	**n = 1***	**n = 1***	
	n (%)	**n (%)**	**n (%)**	**n (%)**	***P***
Maternal complications	2 (7.1)	1 (100.0)	0 (0.0)	0 (0.0)	0.271
No maternal complications or uncomplicated tear	26 (92.9)	0 (0.0)	1 (100.0)	1 (0.0)	0.271

Table 23b. Maternal complications according to anesthesia used in vaginal delivery in women without CHD.

	Anesthesia used in vaginal delivery				
	Epidural anesthesia	**Perineal infiltration**	**Pudendal block**	**Spinal anesthesia**	
	n = 74*	**n = 45***	**n = 1***	**n = 2***	
	n (%)	**n (%)**	**n (%)**	**n (%)**	***P***
Maternal complications	22 (29.7)	8 (17.8)	1 (100.0)	2 (100.0)	0.012
No maternal complications or uncomplicated tear	52 (70.3)	37 (82.2)	0 (0.0)	0 (0.0)	0.012

*In total, anesthesia was used in 31 vaginal deliveries in women with CHD, and in 122 vaginal deliveries in women without CHD, respectively (see Table 16a).

4 Discussion

4-1 Conclusions and discussion

Recommendation of vaginal delivery as mode of choice for women with CHD is based on the different hemodynamic load during vaginal delivery and Caesarean section, resulting in significant cardiovascular changes – e.g. in Caesarean section under spinal anesthesia [Ouzounian 2012] and in more blood loss at delivery in Caesarean section [Karamermer 2007]. Nevertheless, the present study shows a significantly higher rate of Caesarean section in women with CHD in comparison with women without CHD (46.6% vs. 33.6%, $P = 0.012$), which has already been described in previous population based studies, although to a lesser extent. Opotowsky et al. describe Caesarean section rates of 32.2% in women with CHD compared with 26.5% in women without CHD [Opotowsky 2012]. Thompson et al. describe 40.7% compared with 32.3% [Thompson 2015].

A possible explanation for the relatively high rate of Caesarean sections in women without CHD in the present study is that matching was carried out based on the sole characteristic of lacking CHD. Other risk factors more common in a university hospital's patient collective were not taken into account separately. Against expectation, further analysis of common risk factors showed higher rates of diabetes ($P = 0.044$) and preeclampsia ($P = 0.310$) in the supposedly healthy cohort group. The impact of such risk factors as preeclampsia, HELLP syndrome, intrauterine growth restriction and other possible primary diseases can be comprehended by considering the high rate of "obstetric reasons" for primary Caesarean sections (84.3%) in women without CHD. Against expectation, further analysis showed a higher rate of obesity in women with CHD than in women without CHD (6.9% vs. 4.9%, $P = 0.406$). In both women with and without CHD, Caesarean section rate was significantly higher in patients with prior Caesarean section ($P < 0.001$). However, in women with CHD the rate of prior Caesarean section (9.5% vs. 4.9% in women without CHD) as well as the rate of Caesarean section after prior Caesarean section (81.8% vs. 58.8% in women without CHD) was higher, which in combination contributes to the higher overall Caesarean section rate in women with CHD. Knight et al. describe the decline in the use of vaginal birth after Caesarean section (VBAC) in combination with rising rates of primary Caesarean section as a significant driver of the overall Caesarean section rate [Knight 2013]. In the present study, a primary Caesarean section was scheduled in 36.4% of patients with prior Caesarean section in comparison with 15.0% of patients without prior Caesarean section in women with CHD (P = 0.210), and 23.5% of patients with prior Caesarean section in comparison with 2.6% of patients without prior Caesarean section in women without CHD (P = 0.010).

Parity was analyzed as a possible predictor for mode of delivery and pregnancy outcome in patients with and without CHD. In accordance with previous studies [Heffner 2003], multiparity was associated with a higher rate of vaginal delivery in the present study in both women with and without CHD. Primary Caesarean section rate was significantly lower in multiparous patients without CHD only (P = 0.009), whereas in patients with CHD no such effect could be observed and the rate of primary Caesarean section was actually higher than both the secondary Caesarean section rate in multiparous patients as well as the primary Caesarean section rate in nulliparous patients. A possible explanation is the aforementioned high rate of primary Caesarean section after prior Caesarean section in women with CHD.

Additionally, severity of CHD, heart function and group of CHD were analyzed as possible predictors for mode of delivery and pregnancy outcome in patients with CHD only.

The present study suggests that severity of CHD may be useful as a predictor for the risk of a primary Caesarean section. The rate of primary Caesarean sections increases with severity of CHD as could have been expected. It seems probable that women with a history of “severe” CHD will more likely be advised to consider an elective Caesarean section. In addition, due to their own experiences regarding hospitals and their medical past, they might preferably request a planned Caesarean section or a planned vaginal delivery by themselves.

Functional class on the other hand may be useful as a predictor for the risk of a secondary Caesarean section according to the present study. As could have been expected, poor clinical cardiac status seems more likely to lead to a failed attempted vaginal delivery. It could be shown that worsening of the clinical cardiac status correlates with (a) an increasing rate of Caesarean sections altogether, (b) an increasing rate of secondary Caesarean sections altogether as well as (c) an increasing rate of secondary Caesarean sections following induction of labor. Nevertheless, it has to be taken into account that these findings were not significant. The total number of cases in functional class 3 was very limited in the present study (n = 3), limiting the expressiveness of these findings.

Based on the special importance of adequate cardiac output during pregnancy and delivery, patients with certain high-risk lesions are often excluded from recommendation of vaginal delivery [Regitz-Zagrosek 2011, Ruys 2014b]. Generally, these lesions include severe left-sided heart obstruction and presence of mechanical prosthetic valve [Karamermer 2007, Drenthen 2010, Ruys 2014a]. In the present study, no significant difference in mode of delivery for left heart obstruction and subtypes of left heart obstruction, respectively, could be observed. However, the total number of patients with left heart obstruction was limited (n = 17, divided into four subtypes), with no case of left heart obstruction regarded as severe (see Table 6). The only patient with mechanical heart valve included in the present study suffered from postpartum hemorrhage. The only patient with cyanosis included in the present study suffered from a small pulmonary embolism (see 3-4 for single case analyses). Nevertheless, to draw any conclusion more high-risk patients would have to be present.

Analysis of individual indications for primary and secondary Caesarean sections revealed “cardiac reasons” to be a significant factor for primary Caesarean sections only. With regard to secondary Caesarean sections, there was no difference between indications for women with and without CHD. These findings underline the assumption of severity of CHD being a predictor predominantly for primary Caesarean sections.

The present study shows higher rates of induction of labor in women with CHD as has been previously observed. Robertson et al. describe induction rates of 50% in women with heart disease compared with 28% in women without heart disease [Robertson 2012]. In general, the correlation between induction of labor and mode of delivery remains a matter under discussion with conflicting results [Wood 2014]. In the largest systematic review and meta-analysis on the subject to date, including 37 randomized controlled trials, Wood et al. found lower Caesarean section rates following induction of labor. Nevertheless, the authors themselves emphasize the impact of non-treatment effects that might influence these results [Wood 2014]. In studies that describe higher Caesarean section rates following induction of labor, multiple maternal influence factors like gestational age, maternal age and parity have been identified so far [Heffner 2003]. The present study shows higher Caesarean section rates following induction of labor, although not significantly. Analysis of individual indications for induction of labor, however, revealed a significant difference of indications between women with and without CHD. “Logistical reasons” were significantly higher in women with CHD, predominated by inductions “because of long distance” between residence and hospital, an indication completely missing in women without CHD.

In a retrospective cohort study that included over 14.000 patients, Heffner et al. have found that induction of labor, older maternal age and gestational age over 40 weeks each individually increase the risk for Caesarean section in both nulliparous and multiparous women [Heffner 2003]. In the present study, it was analyzed whether – vice versa – gestational age, maternal age and parity have an effect on the rate of Caesarean section in patients with and without performance of induction of labor. The rate of secondary Caesarean section was higher in induced patients from gestational week 36 onwards in patients without CHD, and from gestational week 38 onwards in patients with CHD. However, no general upward trend could be observed, and apart from gestational weeks 38 to 40, number of patients with CHD was 10 or below for the other weeks of gestation. With regard to maternal age, the rate of secondary Caesarean section following induction of labor tended to increase with maternal age. However, using the parameters from Heffner's study, i.e. different age in groups of below 35 years of age, 35 to 39 years of age and 40 years of age and above, total patient number of induced women above 40 years of age was very limited in the present study (n = 3). In nulliparous women, a significantly higher rate of secondary Caesarean section following induction of labor could be observed in women with CHD ($P = 0.033$) and without CHD ($P = 0.001$) alike. In contrast to Heffner et al., who describe a similar relative risk of increase of Caesarean section following induction of labor in nulliparous and multiparous women [Heffner 2003], rate of secondary Caesarean section following induction of labor actually decreased in multiparous women, both with and without CHD, in the present study, in this regard confirming the aforementioned findings of Wood et al.

Pregnancy outcome was similar in women with and without CHD in the present study. There were no adverse fetal outcomes, neither for Caesarean sections nor for vaginal deliveries. In the largest registry on the subject (Registry on Pregnancy and Cardiac Disease (ROPAC)) to date, analyzing data from 1321 pregnant women with structural heart disease, Ruys et al. found similar maternal outcomes and better fetal outcomes in planned vaginal delivery, thus recommending vaginal delivery for women with CHD [Ruys 2014b]. Regarding the much smaller patient collective of the present study, no such difference could be observed. It should be kept in mind, however, that ROPAC included data from 60 hospitals in 28 countries, not all from very well developed countries and different levels of medical care.

The number of cases of SGA (16.4%) was similar to findings in previous studies [Stangl 2008, Cornette 2013]. With regard to the impact of maternal cardiac function in fetal growth restriction, previous studies had lower birth weight and more cases of SGA be expected in women with reduced maternal systolic function [Bamfo 2006]. Higher rates of premature birth ranging from 17.5% [Siu 2001] to 26.2% [Stangl 2008] were reported in previous studies. The present study could not find a significantly higher rate of premature birth in women with CHD than in women without CHD (11.2% vs. 9.2%, $P = 0.526$).

Almost all of the maternal complications found in the present study were obstetric complications (99.2%). There were significantly more obstetric complications in women without CHD ($P = 0.001$). In part, this can be explained by the significantly higher rate of vaginal deliveries in women without CHD, since the vast majority of obstetric complications turned out to be uncomplicated tears in vaginal deliveries. Adjusting the definition of maternal complications by excluding these uncomplicated tears, there were still more maternal complications in women without CHD, although not significantly ($P = 0.130$).

In women with CHD, no significant difference in adjusted maternal complications could be observed for severity of CHD, group of CHD and heart function. Previous studies had found higher rates of complications in patients with high-risk lesions reducing cardiac output [Karamermer 2007, Drenthen 2010, Ruys 2014a], as well as in patients receiving spinal or general anesthesia [Ouzounian 2012, Cauldwell 2016]. In the present study, a significantly more frequent use of epidural anesthesia in women with CHD, as well as a significantly more frequent use of perineal infiltration in women without CHD could be observed with regard to vaginal deliveries. However, there was no difference neither in use of spinal or general anesthesia in women with and without CHD nor in maternal complications following any certain type of anesthesia.

Previous studies have found complicated tears and episiotomies to be more common in nulliparous patients [Christianson 2003]. In women without CHD, rate of adjusted maternal complications was significantly higher in nulliparous women (21.2% vs. 2.2%, $P < 0.001$). Against expectation, in women with CHD there were more adjusted maternal complications in multiparous women, although without significance ($P = 0.299$). An explanation may be the combination of (a) the higher overall rate of vaginal deliveries in women without CHD and (b) the different distribution of Caesarean sections in nulliparous patients. A Caesarean section rate of 49.4% in nulliparous women with CHD compares with 38.7% in multiparous women with CHD and 38.4% in nulliparous women without CHD, amounting to a greater number of possible cases of complicated tears and episiotomies in nulliparous women without CHD as well as in multiparous women with CHD.

Apart from heart failure, postpartum hemorrhage had been identified as the major adverse maternal outcome in previous studies. Percentage ranged from 3.0% [Siu 2001] to 8.4% [Karamermer 2007]. The only case of postpartum hemorrhage in the present study occurred in a case of primary Caesarean section in a high-risk CHD patient with ccTGA and presence of mechanical heart valve. As mentioned earlier, presence of mechanical heart valve is a known risk factor for adverse pregnancy outcome. Anticoagulation treatment to prevent mechanical valve thrombosis caused by the endothelial, hemodynamic and hemostatic factors of Virchow's triad has to be balanced against the risk of bleeding. This is of special concern during pregnancy, given the physiological hypercoagulability in pregnant women [Roudaut 2007, Van Hagen 2015]. In another recent ROPAC study, Van Hagen et al. report a percentage of postpartum hemorrhage in pregnant patients with a mechanical heart valve of 10.4% in comparison with 2.6% in patients without mechanical heart valve (P < 0.001) [Van Hagen 2015].

Generally speaking, congenital heart disease does not seem to have as big of an impact on delivery and pregnancy outcome as might have been expected. The same advances in medical care, particularly in cardiac surgery, that have led to the very growing patient population of pregnant women with CHD are also responsible for a high percentage of women with CHD showing good clinical cardiac status after treatment. Previous studies show equally small numbers of patients in functional classes 3 and 4. Siu et al. describe 4.0%, compared with 2.6% in the present study. This being said, patients in functional classes 3 and 4 will most likely be considered desperately ill and be advised against pregnancy in the first place or be recommended having a termination in case of pregnancy, thus adding to this very outcome.

The analysis of indications for induction of labor showed a significantly higher rate of "planned vaginal delivery", i.e. induction of labor for logistical reasons, in women with CHD. Future studies should delve into this finding more thoroughly, eventually by adding distance from hospital to the matching parameters. It remains to be investigated whether distance from hospital correlates with higher rates of induction of labor in all patients or in women with CHD only. As of now, the assumption could be made that induction of labor was more likely to be performed in women living far away from the hospital in presence of CHD out of concerns about maternal deterioration. Considering the aforementioned numbers of good heart function in women with CHD, such concerns resulting in higher rates of induction of labor [Siu 2001] seem unjustified in most cases. A further investigation into whether distance from hospital is also a risk factor for secondary Caesarean section following induction of labor in all patients or in women with CHD only could corroborate the assumption that induction of labor seems more likely to be performed "prematurely" in women with CHD. In this case, a reduction of planned vaginal delivery – along with a possible reduction of Caesarean sections on maternal request and a possible higher rate of attempted vaginal delivery after prior Caesarean section – may be expedient in reducing the rate of Caesarean sections in women with CHD.

4-2 Strengths and limitations

The present study's main strength is that women with CHD were matched with a large patient collective of women without CHD who delivered during the same period of time at the same center. That way, disturbing factors like differences or changes in obstetrical management could be eliminated.

A limitation of the present study is that it was conducted as a historical cohort study. Data analysis was performed retrospectively based on patient files with the possibility of incorrect data. Furthermore, certain cardiologic data was available for patients with CHD who delivered between 2009 and 2013 only. To increase the significance of the analysis of the data compared, future studies should include the same data for all patients, possibly adding presence of artificial heart valve to the risk factors for maternal complications on which data is collected for both women with and without CHD.

The conclusions of the present study are limited by the fact that study participants were recruited from a specialized tertiary care center for adults with CHD. Presumably, this results in more cases of complex CHD than in the general patient population of women with CHD seen by cardiologists in private practice and other centers. As shown above, more cases of “severe” CHD may also be responsible for more cases of planned Caesarean sections as well as planned vaginal deliveries.

As in every single-center study, patient numbers were limited, especially those of women with CHD belonging to functional classes 3 and 4 as well as those of women with high-risk cardiac lesions, presence of cyanosis or mechanical heart valve and of older maternal age. Although the majority of patients belonging to functional classes 3 and 4 will be advised against pregnancy due to high morbidity and mortality risks in the first place, future studies should involve greater numbers of patients, prospectively collected from multiple centers.

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6 List of abbreviations

A

ACC :	American College of Cardiology
ACHD :	adult congenital heart disease
APGAR* :	Appearance, Pulse, Grimace, Activity, Respiration (*backronym of the surname of the APGAR score's inventor, Virginia Apgar)
AS :	aortic stenosis
ASD :	atrial septal defect

B

BAV :	bicuspid aortic valve

C

ccTGA :	congenitally corrected transposition of the great arteries
CHD :	congenital heart disease
CoA :	coarctation of the aorta
CTG :	cardiotocography

D

DORV :	double outlet right ventricle

E

ESC :	European Society of Cardiology

F

FBN1 :	Fibrillin 1
FBS :	fetal blood sampling
FFP :	fresh frozen plasma

G

g :	gram
GATA4 :	GATA* transcription factor 4 (*DNA sequence)

H

Hb :	hemoglobin
HELLP :	Hemolysis, Elevated Liver enzymes, Low Platelet count
HOCM :	hypertrophic obstructive cardiomyopathy

I

ICD :	implantable cardioverter defibrillator

K

KRAS :	Kirsten RAt Sarcoma

M

ml :	milliliter
MVP :	mitral valve prolapse

	MYH6 :	Myosin, Heavy Chain 6
N		
	NKX2.5 :	Natural Killer-like 2 homeobox 5
	NOTCH1 :	Notch homolog 1, translocation-associated (Drosophila)
P		
	PFO :	patent foramen ovale
	pH :	potentia hydrogenii
	PPH :	postpartum hemorrhage
	PS :	pulmonary stenosis
	PTPN11 :	Protein Tyrosine Phosphatase, Non-Receptor Type 11
R		
	RAF1 :	Rapidly Accelerated Fibrosarcoma 1
	RCC :	red cell concentrate
	ROPAC :	Registry on Pregnancy and Cardiac Disease
S		
	SAP :	Systemanalyse und Programmentwicklung
	SAS :	subaortic stenosis
	SD :	standard deviation
	SGA :	small for gestational age
	SOS1 :	Son Of Sevenless homolog 1
	SpO2 :	saturation of peripheral oxygen
T		
	TGA :	transposition of the great arteries
	TOF :	tetralogy of Fallot
	TOF/APV :	tetralogy of Fallot with absent pulmonary valve
	TrA :	truncus arteriosus
U		
	UCLA :	University of California, Los Angeles
V		
	VBAC :	vaginal birth after Caesarean section
	VSD :	ventricular septal defect
Z		
	ZAHARA :	Zwangerschap bij Aangeboren HARtAfwijkingen

PLOS ONE

RESEARCH ARTICLE

Mode of Delivery and Pregnancy Outcome in Women with Congenital Heart Disease

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Abstract

Background

Advances in cardiac surgery and congenital cardiology have led to an increasing number of women with congenital heart disease (CHD) reaching childbearing age. In general, cardiologists recommend vaginal delivery for women with CHD to avoid complications from Caesarean section as many women with CHD tolerate vaginal delivery well.

Methods and Results

This is a single-center study comparing mode of delivery, pregnancy outcome, indications for Caesarean section and induction of labor between women with and without CHD. A historical cohort study was conducted including 116 patients with CHD. An individual threefold matching with 348 women without CHD was carried out. Caesarean section was performed in 46.6% of pregnancies with CHD (33.6% without CHD, $P = 0.012$). Primary Caesarean section increases with severity of CHD ($P = 0.036$), 33.3% of women with CHD had primary planned Caesarean section due to cardiac reasons. Induction of labor was performed in 45.7% of attempted vaginal deliveries in women with CHD (27.9% without CHD, $P = 0.001$). Lower mean birth weight ($P = 0.004$) and Small for Gestational Age (SGA) ($P < 0.001$) were more common in women with CHD. One CHD patient suffered from postpartum hemorrhage.

Conclusions

Concerns about maternal deterioration resulting in higher rates of induction of labor seem unjustified in most cases. Along with a possible reduction of Caesarean section on maternal request, a reduction of planned vaginal delivery may be expedient in reducing the rate of Caesarean section in women with CHD.

Competing Interests: The authors have declared that no competing interests exist.

Introduction

Advances in cardiology and cardiac surgery have led to a steadily increasing number of adults with congenital heart disease (CHD), including women, reaching childbearing age. Physiological hemodynamic changes during pregnancy and delivery are of special concern in this growing patient population. While many recent publications have recommended vaginal delivery as mode of choice for women with CHD [1–3], Caesarean section rate remains higher in these patients than in the normal population [3–5]. With Caesarean section rate among women with CHD varying widely between countries, Germany ranks above international average [3].

The objectives of the present single-center study were to compare mode of delivery, pregnancy outcome and indications for Caesarean section and induction of labor between women with and without CHD. Results from one of the large centers with regard to delivery in women with CHD may also help to ascertain the reasons for the comparatively high Caesarean section rate among women with CHD in Germany.

Materials and Methods

A historical cohort study was conducted based on patient files, including 116 patients with CHD from the German Heart Centre Munich who delivered between January 2005 and December 2013 at the Klinikum rechts der Isar, Munich. An individual threefold matching with a total of 348 women without CHD was carried out, using the parameters maternal age, gravidity, parity, and year of delivery.

The study protocol was approved by the Ethics Committee of Klinikum rechts der Isar, Medizinische Fakultaet, Technical University of Munich (approval number 433/13).

CHD patients provided written consent to participate in the study.

Women with CHD were clinically classified by severity of CHD according to the American College of Cardiology [6] and functional class according to Perloff [7]. As for severity of CHD, primary cardiac main diagnosis (native CHD) was decisive for classification. As for functional class, the clinical cardiac status after surgical or interventional repair as evaluated last before delivery was decisive.

Indications for Caesarean sections were differentiated into cardiac, obstetric and other reasons. Cardiac reasons were defined as "poor heart function" and "worsening of heart function", respectively. Obstetric reasons were defined as "fetal safety reasons" and, in the case of secondary Caesarean sections, "failure to progress in labor". It should be noted, however, that this differentiation can be somewhat vague in clinical practice, given the great number of combined indications. The indication for Caesarean section as stated in the patient file by the obstetrician in charge was decisive.

Data analysis was performed using SPSS software version 22.0 (SPSS Inc., IBM). Chi square tests were used for comparing differences in categorical data between independent patient groups. Fisher's exact tests were applied if any expected cell count was < 5. Student t tests were used for comparing differences in continuous data between independent patient groups. According to convention, P values < 0.05 were considered statistically significant.

Results

Characteristics of the study population

Maternal baseline characteristics in women with CHD are outlined in Table 1. Since maternal age and parity were among the matching parameters, mean maternal age and percentage of nulliparous and multiparous were the same in women without CHD.

Table 1. Maternal baseline characteristics in women with CHD.

		n = 116
		n (%)
Age (years) (SD)		29.7 (±4.5)
Parity		
	Nulliparous	85 (73.3)
	Multiparous	31 (26002E7)
Severity of CHD (according to ACC)		
	Simple	30 (25.9)
	Moderate	59 (50.9)
	Severe	27 (23.2)
Functional class (according to Perloff)		
	I	47 (40.5)
	II	66 (56.9)
	III	3 (2.6)
	IV	0 (0.0)
Diagnosis		
	Post-tricuspid shunts:	9 (7.8)
	VSD	
	Pre-tricuspid shunts:	17 (14.7)
	ASD, PFO	
	Left heart obstructions:	17 (14.7)
	AS, BAV, CoA, SAS	
	Right heart obstructions:	33 (28.4)
	DORV, PS, TOF	
	Complex anomalies:	24 (20.7)
	ccTGA, TGA, TOF/APV, TrA	
	Hereditary:	7 (6.0)
	Marfan's syndrome	
	Congenital rhythm anomalies:	2 (1.7)
	atrioventricular block	
	Other:	7 (6.0)
	aortic aneurysm, Ebstein's anomaly, congenital form of HOCM, MVP	

AS = aortic stenosis, ASD = atrial septal defect, BAV = bicuspid aortic valve, ccTGA = congenitally corrected transposition of the great arteries, CoA = coarctation of the aorta, DORV = double outlet right ventricle, HOCM = hypertrophic obstructive cardiomyopathy, MVP = mitral valve prolapse, PFO = patent foramen ovale, PS = pulmonary stenosis, SAS = subaortic stenosis, TGA = transposition of the great arteries, TOF = tetralogy of Fallot, TOF/APV = tetralogy of Fallot with absent pulmonary valve, TrA = truncus arteriosus, VSD = ventricular septal defect

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Classification showed that severity of CHD and functional class did not correspond: With regard to severity, approximately half of the cases were considered "moderate", with approximately a quarter of cases being considered "simple"and "severe"each [6]. With regard to the clinical cardiac status, 97.4% of cases belonged to functional classes I and II (with the bigger

Table 2. Maternal risk factors.

		with CHD	without CHD	
		n = 116	n = 348	
		n (%)	n (%)	*P*
Body mass index (SD)		23,20 (±3,95)	22,76 (±3,86)	0.298
	≤17.5	0 (0.0)	9 (2.6)	0.120
	≥30.0	8 (6.9)	17 (4.9)	0.406
Smoking		1 (0.9)	6 (1.7)	0.686
Preeclampsia		1 (0.9)	11 (3.2)	0.310
Diabetes		2 (1.7)	23 (6.6)	0.044
	Preexisting	0 (0.0)	3 (0.9)	0.577
	Gestational	2 (1.7)	20 (5.7)	0.077
Prior C-section		11 (9.5)	17 (4.9)	0.072

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share in functional class II), and only 2.6% to functional class III, with no cases in a possible functional class IV [7].

Maternal risk factors for complications during and outcome of pregnancy are outlined in Table 2.

Body mass index (BMI) was slightly higher in women with CHD. Smoking, preeclampsia and diabetes were more common in women without CHD, with a significant difference for diabetes only ($P = 0.044$). A total of 9.5% of patients with prior Caesarean section in women with CHD compared with 4.9% in women without CHD ($P = 0.072$).

Mode of delivery

Details pertaining to mode of delivery are shown in Table 3. The rate of Caesarean section was significantly higher in women with CHD. Caesarean section was performed in 46.6% of pregnancies in women with CHD, compared with 33.6% of pregnancies in women without CHD ($P = 0.012$). The rate of primary Caesarean section, defined as "planned Caesarean section", as well as the rate of secondary Caesarean section, defined as "Caesarean section following spontaneous onset of labor/failed attempted vaginal delivery", was higher in women with CHD.

The rate of spontaneous vaginal delivery (44.8% vs. 56.0%, $P = 0.036$) as well as the rate of operative vaginal delivery (8.6% vs. 10.4%, $P = 0.590$) was lower in women with CHD.

Mode of delivery was compared in all multiparous patients according to prior Caesarean section (see Tables 4 and 5). In both women with and without CHD, Caesarean section rate was significantly higher in multiparous patients with prior Caesarean section compared with

Table 3. Mode of delivery.

			with CHD	without CHD	
			n = 116	n = 348	
			n (%)	n (%)	*P*
Vaginal delivery			62 (53.4)	231 (66.4)	0.012
	Spontaneous		52 (44.8)	195 (56.0)	0.036
	Operative vaginal		10 (8.6)	36 (10.4)	0.590
		Vacuum extraction	10 (8.6)	33 (9.5)	0.782
		Forceps	0 (0.0)	3 (0.9)	0.577
C-section			54 (46.6)	117 (33.6)	0.012
	Primary		24 (20.7)	51 (14.7)	0.126
	Secondary		30 (25.9)	66 (18.9)	0.112

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Table 4. Mode of delivery according to prior Caesarean section in women with CHD.

		Prior C-section	No prior C-section	
		n = 11*	n = 20*	
		n (%)	n (%)	*P*
Vaginal delivery		2 (18.2)	17 (85.0)	< 0.001
C-section		9 (81.8)	3 (15.0)	< 0.001
	Primary	4 (36.4)	3 (15.0)	0.210
	Secondary	5 (45.5)	0 (0.0)	0.003

*Only patients with a possible prior Caesarean section, i.e. multiparous patients (n = 31 in patients with CHD), were included.

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Table 5. Mode of delivery according to prior Caesarean section in women without CHD.

		Prior C-section	No prior C-section	
		n = 17*	n = 76*	
		n (%)	n (%)	*P*
Vaginal delivery		7 (41.2)	67 (88.2)	< 0.001
C-section		10 (58.8)	9 (11.8)	< 0.001
	Primary	4 (23.5)	2 (2.6)	0.010
	Secondary	6 (35.3)	7 (9.2)	0.012

*Only patients with a possible prior Caesarean section, i.e. multiparous patients (n = 93 in patients without CHD), were included.

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multiparous patients without prior Caesarean section (81.8% vs. 15.0% in women with CHD, $P < 0.001$, and 58.8% vs. 11.8% in women without CHD, $P < 0.001$, respectively).

In women with CHD, mode of delivery was compared according to division in groups for severity of CHD and functional class (see Tables 6 and 7). There was no correlation between

Table 6. Mode of delivery according to severity of CHD.

		Severity of CHD			
		Simple	Moderate	Severe	
		n = 30	n = 59	n = 27	
		n (%)	n (%)	n (%)	*P*
Vaginal delivery		15 (50.0)	35 (59.3)	12 (44.4)	0.398
C-section		15 (50.0)	24 (40.7)	15 (55.6)	0.398
	Primary	3 (10.0)	11 (18.7)	10 (37.1)	0.036
	Secondary	12 (40.0)	13 (22.0)	5 (18.5)	0.114

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Table 7. Mode of delivery according to heart function in women with CHD.

		Functional class			
		I	II	III	
		n = 47	n = 66	n = 3	
		n (%)	n (%)	n (%)	*P*
Vaginal delivery		30 (63.8)	31 (47.0)	1 (33.3)	0.146
C-section		17 (36.2)	35 (53.0)	2 (66.7)	0.146
	Primary	8 (17.0)	16 (24.2)	0 (0.0)	0.600
	Secondary	9 (19.2)	19 (28.8)	2 (66.7)	0.111

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Table 8. Indications for primary Caesarean sections.

		with CHD	without CHD	
		n = 24	n = 51	
		n (%)	n (%)	*P*
Cardiac reason		8 (33.3)	-	< 0.001
Obstetric reason		9 (37.5)	43 (84.3)	< 0.001
Other reason		7 (29.2)	8 (15.7)	0.219
	Maternal request	4 (16.7)	5 (9.8)	0.455

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severity of CHD and mode of delivery in general ($P = 0.398$). However, detailed analysis showed that the number of primary Caesarean sections increases significantly with severity ($P = 0.036$) while the number of secondary Caesarean sections decreases ($P = 0.114$).

In the case of functional classes, the ratio of vaginal delivery and Caesarean section tended to invert according to worsening of the clinical cardiac status ($P = 0.146$).

Indications for primary and secondary Caesarean sections were examined individually (see Tables 8 and 9).

Cardiac reasons came to 33.3% of primary Caesarean sections in women with CHD. Obstetric reasons for primary Caesarean sections were significantly higher in women without CHD ($P < 0.001$). There was no significant difference in "other reasons" for primary Caesarean sections in women with and without CHD ($P = 0.219$). In both cases, Caesarean section on maternal request predominated with a relative percentage of 57.1% (n = 4 out of 7) and 62.5% (n = 5 out of 8), respectively.

In contrast to primary Caesarean sections, there was no significant difference in indications for secondary Caesarean sections in women with and without CHD. Cardiac reasons came to no more than 6.7% of secondary Caesarean sections in women with CHD. In women with and without CHD, obstetric reasons predominated clearly (90.0% vs. 93.9%).

Induction of labor

Excluding primary Caesarean sections (20.7% vs. 14.7%), vaginal delivery was attempted in 79.3% of pregnancies in women with CHD and 85.3% of pregnancies in women without CHD. Details pertaining to induction of labor are shown in Table 10. Induction of labor was performed in 45.7% of attempted vaginal deliveries in women with CHD, compared with 27.9% in women without CHD ($P = 0.001$).

As can be seen in Tables 11 and 12, performance of induction of labor was associated with higher rates of secondary Caesarean section in both women with and without CHD. In women with CHD, secondary Caesarean section rate was 24.0% without induction of labor and 42.9% following induction ($P = 0.055$). In women without CHD, secondary Caesarean section rate was 17.8% without induction of labor and 33.7% following induction ($P = 0.003$).

Table 9. Indications for secondary Caesarean sections.

	with CHD	without CHD	
	n = 30	n = 66	
	n (%)	n (%)	*P*
Cardiac reason	2 (6.7)	-	0.095
Obstetric reason	27 (90.0)	62 (93.9)	0.674
Other reason	1 (3.3)	4 (6.1)	1.000

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Table 10. Induction of labor.

			with CHD	without CHD	
			n = 92*	n = 297*	
			n (%)	n (%)	*P*
Induction of labor			42 (45.7)	83 (27.9)	0.001
Indication for induction of labor					
	Medical reason		27 (64.3)	82 (98.8)	< 0.001
	Logistical reason		15 (35.7)	1 (1.2)	< 0.001
		"because of long distance"	13 (31.0)	0 (0.0)	< 0.001

*To avoid falsification of results due to different rates of primary Caesarean sections in women with and without CHD (20.7% vs. 14.7%), only cases of attempted vaginal delivery (n = 389) were examined. 24 and 51 primary Caesarean sections, respectively, were excluded.

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Table 11. Mode of delivery according to performance of induction of labor in women with CHD.

	Induction performed	Induction not performed	
	n = 42*	n = 50*	
	n (%)	n (%)	*P*
Vaginal delivery	24 (57.1)	38 (76.0)	0.055
Secondary C-section	18 (42.9)	12 (24.0)	0.055

*As in Table 10, only cases of attempted vaginal delivery (n = 92 in patients with CHD) were examined.

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Indications for induction of labor differed with high significance in women with and without CHD. In women without CHD, 98.8% of inductions of labor were performed for medical reasons, compared with only 64.3% in women with CHD ($P < 0.001$). Of the remaining 35.7% of inductions of labor which were performed for logistical reasons in women with CHD, a clear majority was performed "because of long distance"between the patient's place of residence and our hospital, the relative percentage being 86.7% (n = 13 out of 15).

Mode of delivery following induction of labor was compared according to the different categories of severity of CHD and functional class, respectively (see Tables 13 and 14). As for severity of CHD, there was no correlation between mode of delivery following induction of labor ($P = 0.843$). In the case of functional classes, the ratio of vaginal delivery and secondary Caesarean sections tended to invert according to worsening of heart function ($P = 0.254$).

Pregnancy outcome

Pregnancy outcome is outlined in Table 15. There were no cases of maternal, perinatal or neonatal mortality, and no cases of adverse neonatal outcome in the present study. There was one

Table 12. Mode of delivery according to performance of induction of labor in women without CHD.

	Induction performed	Induction not performed	
	n = 83*	n = 214*	
	n (%)	n (%)	P
Vaginal delivery	55 (66.3)	176 (82.2)	0.003
Secondary C-section	28 (33.7)	38 (17.8)	0.003

*As in Table 10, only cases of attempted vaginal delivery (n = 297 in patients without CHD) were examined.

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Table 13. Mode of delivery following induction of labor according to severity of CHD.

	Severity of CHD			
	Simple	Moderate	Severe	
	n = 14*	n = 21*	n =7*	
	n (%)	n (%)	n (%)	*P*
Vaginal delivery	7 (50.0)	13 (61.9)	4 (57.1)	0.843
Secondary C-section	7 (50.0)	8 (38.1)	3 (42.9)	0.843

*Total number of induced patients in each category

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Table 14. Mode of delivery following induction of labor according to heart function in women with CHD.

	Functional class			
	I	II	III	
	n = 19*	n = 21*	n =2*	
	n (%)	n (%)	n (%)	*P*
Vaginal delivery	12 (63.2)	12 (57.1)	0 (0.0)	0.254
Secondary C-section	7 (36.8)	9 (42.9)	2 (100.0)	0.254

*Total number of induced patients in each category

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case of adverse maternal outcome in the form of postpartum hemorrhage in a patient with CHD.

Overall, mean pregnancy duration and the rate of premature birth were similar in women with and without CHD. Lower mean birth weight ($P = 0.004$) and Small for Gestational Age (SGA) ($P < 0.001$) were significantly more common in women with CHD.

Discussion

Recommendation of vaginal delivery as mode of choice for women with CHD is based on different hemodynamic load during vaginal delivery and Caesarean section, resulting in significant cardiovascular changes—e.g. in Caesarean section under spinal anesthesia [8] and in more blood loss at delivery in Caesarean section [2]. Nevertheless, the present study shows a significantly higher rate of Caesarean section in women with CHD in comparison with women without CHD (46.6% vs. 33.6%, $P = 0.012$), which has already been described in

Table 15. Pregnancy outcome.

	with CHD	without CHD	
	n = 116	n = 348	
	n (%)	n (%)	*P*
Postpartum hemorrhage	1 (0.9)	0 (0.0)	0.250
Pregnancy duration (weeks) (SD)	38.7 (±2.3)	38.7 (±2.0)	0.054
Premature birth	13 (11.2)	32 (9.2)	0.526
Birth weight (g) (SD)	3092 (±588)	3267 (±547)	0.004
SGA	19 (16.4)	8 (2.3)	< 0.001
APGAR score (after 1 / 5 / 10 min)	8.32 / 9.21 / 9.65	8.25 / 9.18 / 9.65	
Arterial cord pH (SD)	7.28 (±0.08)	7.26 (±0.09)	0.017

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previous population based studies, although to a lesser extent. Opotowsky et al. describe Caesarean section rates of 32.2% in women with CHD compared with 26.5% in women without CHD [4]. Thompson et al. describe 40.7% compared with 32.3% [5]. A possible explanation for the relatively high rate of Caesarean sections in women without CHD in the present study is that matching was carried out based on the sole characteristic of lacking CHD. Other risk factors more common in a university hospital's patient collective were not taken into account separately. Against expectation, further analysis of common risk factors showed higher rates of diabetes ($P = 0.044$) and preeclampsia ($P = 0.310$) in the supposedly healthy cohort group. The impact of such risk factors as preeclampsia, HELLP syndrome, intrauterine growth restriction and other possible primary diseases can be comprehended by considering the high rate of "obstetric reasons" for primary Caesarean sections (84.3%) in women without CHD. Against expectation, further analysis showed a higher rate of obesity in women with CHD than in women without CHD (6.9% vs. 4.9%, $P = 0.406$). The rate of prior Caesarean section as well as the rate of Caesarean section after prior Caesarean section was higher in women with CHD, which in combination contributes to the higher overall Caesarean section rate in women with CHD.

Severity of CHD and heart function were analyzed as possible predictors for mode of delivery and pregnancy outcome.

The present study suggests that severity of CHD may be useful as a predictor for the risk of a primary Caesarean section. The rate of primary Caesarean sections increases with severity of CHD as could have been expected. It seems probable that women with a history of "severe" CHD will more likely be advised to consider an elective Caesarean section. In addition, due to their own experiences regarding hospitals and their medical past, they might preferably request a planned Caesarean section or a planned vaginal delivery by themselves.

Functional class on the other hand may be useful as a predictor for the risk of a secondary Caesarean section according to the present study. As could have been expected, poor clinical cardiac status seems more likely to lead to a failed attempted vaginal delivery. It could be shown that worsening of the clinical cardiac status correlates with (a) an increasing rate of Caesarean sections altogether, (b) an increasing rate of secondary Caesarean sections altogether as well as (c) an increasing rate of secondary Caesarean sections following induction of labor. Nevertheless, it has to be taken into account that these findings were not significant. The total number of cases in functional class III was very limited in the present study (n = 3), limiting the expressiveness of these findings.

Analysis of individual indications for primary and secondary Caesarean sections revealed "cardiac reasons" to be a significant factor for primary Caesarean sections only. With regard to secondary Caesarean sections, there was no difference between indications for women with and without CHD. These findings underline the assumption of severity of CHD being a predictor predominantly for primary Caesarean sections.

The present study shows higher rates of induction of labor in women with CHD as has been previously observed. Robertson et al. describe induction rates of 50% in women with heart disease compared with 28% in women without heart disease [1]. In general, the correlation between induction of labor and mode of delivery remains a matter under discussion with conflicting results [9]. In the largest systematic review and meta-analysis on the subject to date, including 37 randomized controlled trials, Wood et al. found lower Caesarean section rates following induction of labor. Nevertheless, the authors themselves emphasize the impact of non-treatment effects that might influence these results [9]. In studies that describe higher Caesarean section rates following induction of labor, multiple maternal influence factors like parity, maternal age and gestational age have been identified so far [10]. The present study shows higher Caesarean section rates following induction of labor, although not significantly.

Analysis of individual indications for induction of labor, however, revealed a significant difference of indications between women with and without CHD. “Logistical reasons” were significantly higher in women with CHD, predominated by inductions “because of long distance” between residence and hospital, an indication completely missing in women without CHD.

Pregnancy outcome was similar in women with and without CHD in the present study. There were no adverse fetal outcomes, neither for Caesarean sections nor for vaginal deliveries. In the largest registry on the subject (Registry on Pregnancy and Cardiac Disease (ROPAC)) to date, analyzing data from 1321 pregnant women with structural heart disease, Ruys et al. found similar maternal outcomes and better fetal outcomes in planned vaginal delivery, thus recommending vaginal delivery for women with CHD [3]. Regarding the much smaller patient collective of the present study, no such difference could be observed. It should be kept in mind, however, that ROPAC included data from 60 hospitals in 28 countries, not all from very well developed countries and different levels of medical care.

The number of cases of SGA (19%) was similar to findings in previous studies [11, 12]. With regard to the impact of maternal cardiac function in fetal growth restriction, former studies had lower birth weight and more cases of SGA be expected in women with reduced maternal systolic function [13]. Higher rates of premature birth ranging from 17.5% [14] to 26.2% [11] were reported in previous studies. The present study could not find a significantly higher rate of premature birth in women with CHD than in women without CHD (11.2% vs. 9.2%, $P = 0.526$).

Apart from heart failure, postpartum hemorrhage had been identified as the major adverse maternal outcome in previous studies. Percentage ranged from 3% [14] to 8.4% [2]. The only case of postpartum hemorrhage in the present study occurred in a case of primary Caesarean section in a woman with CHD.

Generally speaking, congenital heart disease does not seem to have as big of an impact on delivery and pregnancy outcome as might have been expected. The same advances in medical care, particularly in cardiac surgery, that have led to the very growing patient population of pregnant women with CHD are also responsible for a high percentage of women with CHD showing good clinical cardiac status after treatment. Previous studies show equally small numbers of patients in functional classes III and IV. Siu et al. describe 4.0%, compared with 2.6% in the present study. This being said, patients in functional classes III and IV will most likely be considered desperately ill and be advised against pregnancy in the first place or be recommended having a termination in case of pregnancy, thus adding to this very outcome.

The analysis of indications for induction of labor showed a significantly higher rate of “planned vaginal delivery”, i.e. induction of labor for logistical reasons, in women with CHD. Future studies should delve into this finding more thoroughly, eventually by adding distance from hospital to the matching parameters. It remains to be investigated whether distance from hospital correlates with higher rates of induction of labor in all patients or in women with CHD only. As of now, the assumption could be made that induction of labor was more likely to be performed in women living far away from the hospital in presence of CHD out of concerns about maternal deterioration. Considering the aforementioned numbers of good heart function in women with CHD, such concerns resulting in higher rates of induction of labor [14] seem unjustified in most cases. A further investigation into whether distance from hospital is also a risk factor for secondary Caesarean section following induction of labor in all patients or in women with CHD only could corroborate the assumption that induction of labor seems more likely to be performed “prematurely” in women with CHD. In this case, a reduction of planned vaginal delivery—along with a possible reduction of Caesarean sections on maternal request and a possible higher rate of attempted vaginal delivery after prior Caesarean section—may be expedient in reducing the rate of Caesarean sections in women with CHD.

Strengths and limitations

The present study's main strength is that women with CHD were matched with a large patient collective of women without CHD who delivered during the same period of time at the same center. That way, disturbing factors like differences or changes in obstetrical management could be eliminated.

A limitation of the present study is that it was conducted as a historical cohort study. Data analysis was performed retrospectively based on patient files with the possibility of incorrect data. The conclusions of the present study are limited by the fact that study participants were recruited from a specialized tertiary care center for adults with CHD. Presumably, this results in more cases of complex CHD than in the general patient population of women with CHD seen by cardiologists in private practice and other centers. As shown above, more cases of "severe" CHD may also be responsible for more cases of planned Caesarean sections as well as planned vaginal delivery. As in every single-center study, patient numbers were limited, especially those of women with CHD belonging to functional classes III and IV. Although the majority of patients belonging to functional classes III and IV will be advised against pregnancy due to high morbidity and/or mortality risks in the first place, future studies should involve greater numbers of patients, prospectively collected from multiple centers.

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