Herzschr Elektrophys 2021 · 32:174–179
https://doi.org/10.1007/s00399-021-00754-7
Received: 6 January 2021
Accepted: 16 March 2021
Published online: 1 April 2021

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Arrhythmic risk during pregnancy in patients with congenital heart disease

Survival of patients with congenital heart disease (CHD) has significantly increased in recent decades, with over 90% of children with CHD reaching adulthood in developed countries [15]. One of the central issues in the clinical management of adult CHD is rhythm disturbances [34], including atrial and ventricular tachyarrhythmias, bradyarrhythmias, and sudden cardiac death, either caused intrinsically by the structural abnormality itself, or attributed to long-standing pressure/volume overload, cyanosis, ischemia, and the presence of surgical scars [11]. Clinical arrhythmia tolerance is highly variable, ranging from asymptomatic "benign" rhythm disturbances to poorly tolerated or even fatal arrhythmias. Overall, arrhythmias account for significant morbidity and mortality in adult CHD patients.

Physiological changes in pregnancy and their effects on the cardiovascular system

Already during early pregnancy the heart must adapt to enhanced volume load, as blood volume increases disproportionally to the number of red blood cells [4]. Cardiac output is raised significantly with elevation of heart rate, end-diastolic volume, and thus stroke volume to accommodate the increase in basal oxygen consumption that arises later in pregnancy [3, 21]. Heart rate variability decreases [31], possibly associated with activation of sympathetic and reduction in vagal tone, and ion channel remodelling in sinoatrial node cells [6]. Systemic vascular resistance progressively decreases, but mean arterial pressure remains relatively constant [21]. At the time of delivery, the cardiovascular system faces large hemodynamic fluctuations: around 500 mL of blood is re-distributed with each uterine contraction, and venous return is further increased at the time of vena cava decompression, while blood loss successively totals up to 1000 mL [33]. Parallel to functional hemodynamic changes, pregnancy also induces structural myocardial remodelling, which begins with atrial enlargement in the first trimester, associated with increased preload [27]. Increased preload together with increased stroke work may also be responsible for the eccentric hypertrophy of the left ventricle occurring during pregnancy [27], with ventricular mass elevation persisting until months after delivery [21].

These significant (yet physiological) alterations lead to increased arrhythmia susceptibility, including premature beats and non-sustained arrhythmia in healthy pregnant women [20]. CHD "alone" is associated with scarring, pressure/volume overload, increased chamber dimensions, and altered myocardial structure (including fibrosis), all of which can contribute to conduction velocity inhomogeneity and dispersion in refractoriness, thus facilitating re-entry circuits, enhanced automaticity, and triggered activity already in a non-pregnant state [11]. Unsurprisingly, therefore, arrhythmias play an especially prominent role among pregnancy-associated complications in CHD patients.

Incidence of arrhythmias

In women with any kind of cardiovascular disease (congenital or acquired), sustained arrhythmias during the ante-, peri-, and post-partum periods are not uncommon, affecting approximately 7–9% of pregnancies, with the highest risk during the ante-partum period [22, 28, 30]. In comparison, the occurrence of sudden cardiac death or cardiac arrest is rare with an incidence of 0.6% [28, 30]. Compared to healthy women, women with CHD are more likely to die during admission for delivery [23], and arrhythmias are the main pregnancy-associated cardiac complication in women with CHD, manifesting as sustained symptomatic arrhythmia requiring treatment in 3–8% of pregnancies [5, 13, 16, 17, 25, 30]. In these patients, non-sustained symptomatic arrhythmias requiring treatment may be even more frequent, and account for around 60–80% of all arrhythmias during pregnancy, delivery, and post-partum [16, 25].

Asymptomatic rhythm disturbances affect nearly all pregnant women with CHD. A prospective study performing Holter ECG in pregnant CHD patients and pregnant control patients revealed that, while both groups demonstrated a high (around 90%) incidence of

premature atrial contractions, premature ventricular contractions (PVC) and PVC couplets were significantly more frequent in CHD patients than in healthy controls (incidence of 94% and 31% vs 74% and 0%, respectively) [22]. Moreover, tachyarrhythmias were unique to the CHD group with an incidence of 26% overall and 14% for non-sustained asymptomatic ventricular tachycardia (VT) [22]. Consistently, a multicentre study conducted in Japan reported a similar prevalence of 27% of any kind of arrhythmia (sustained or non-sustained tachy- or bradyarrhythmia) in pregnant women with corrected CHD [32].

Reports regarding arrhythmia risk during admission for delivery are inconsistent. A nationwide US study with 30,500 CHD patients admitted for delivery between 1998 and 2007 demonstrated arrhythmia occurrence in 2.6% of women with CHD, which was significantly more frequent compared to the incidence of 0.21% in women without CHD [23]. Similarly, a study examining around 1300 CHD patients admitted for delivery in New York State, US, between 2000 and 2014 demonstrated arrhythmia occurrence in 3.7% of women with CHD [24]. However, a retrospective study with over 3400 CHD patients admitted for delivery in California, US, between 2005 and 2011 observed a lower incidence of under 0.5% for atrial and serious ventricular arrhythmias [10]. Multivariate adjustment revealed greater odds for both atrial and ventricular arrhythmias for CHD patients compared to patients without CHD [10]. As the above studies applied inconsistent definitions for arrhythmias, the differences in arrhythmia incidence reported may be due, in part, to in- or exclusion of specific arrhythmia types (especially bradyarrhythmias and premature beats).

Similar to the ante-, peri-, and immediately post-partum periods, the most common cardiac event in women with CHD late after pregnancy (>6 months post-partum) is arrhythmias, which occurred in 5–8% of women and originated mostly from the atrium [2, 12].

It becomes clear that arrhythmia incidence during pregnancy in women with CHD depends significantly on the time points investigated (ante-/peri-/post-partum) and the definition of arrhythmia applied, which is especially variable regarding sustained/non-sustained arrhythmia, symptomatic/asymptomatic arrhythmia, requirement of treatment, and in- or exclusion of premature beats and bradyarrhythmia.

Arrhythmia subtypes and clinical relevance

Pregnancy-related rhythm disturbances arise from both the atria and the ventricles in women with CHD (**Fig. 1**). However, reports regarding the proportions of premature beats, atrial tachyarrhythmias, ventricular tachyarrhythmias, and bradyarrhythmias are inconsistent, possibly due to differing arrhythmia definitions and study designs. As most studies concentrated on sustained or symptomatic arrhythmias, premature beats were often not reported. In prospective Holter ECG examinations, Niwa et al. revealed high incidences of over 90% for premature beats and couplets originating from both the atrium and the ventricle [22], while Opotowsky et al. reported a much lower incidence of 8% for premature beats, presumably due to the retrospective nature of the study, which considered only diagnoses encoded in medical charts [23].

The atria seem to be the origin of most tachyarrhythmias in the ante-, peri-, and post-partum periods [12, 23, 30, 32]. While more specific classification of these atrial tachyarrhythmias is often lacking, previous reports indicate that atrial fibrillation may be more common than atrial flutter or other forms of SVT [23, 32]. Among atrial tachyarrhythmias, SVT seems to be especially poorly tolerated. A previous report demonstrated a significant increase in maternal symptoms, such as dizziness, palpitations, fatigue, dyspnoea, and chest pain, during SVT episodes in pregnancy compared to pre-pregnancy SVT episodes [19]. Symptoms and/or heart failure resulting from SVT frequently necessitated emergency treatment [22].

Non-sustained and sustained ventricular arrhythmias comprise less than 30% of all pregnancy-related arrhythmic events (**Fig. 1** and [12, 16, 22, 23, 30, 32]). Non-sustained VT appears to be mostly asymptomatic [22], but may demonstrate a readiness for higher-grade, potentially life-threatening arrhythmias such as sustained VT and ventricular fibrillation. Therefore, despite the comparable rarity of documented ventricular arrhythmias, they may have detrimental effects on mother and child, and patients presenting with lower-grade ventricular arrhythmias should therefore be carefully evaluated.

Bradyarrhythmias including sinus node dysfunction and conduction disturbances have not been regularly assessed. They appear to account for 5–20% of all rhythm disturbances (**Fig. 1** and [22, 23, 30, 32]) and are mostly already present before pregnancy [32]. Device-related treatment has frequently taken place before pregnancy, so that these bradyarrhythmias often pose less relevance to mother or child than tachyarrhythmias.

The incidence of foetal and neonatal adverse events is higher in pregnant women with CHD compared to women without CHD [24]. In pregnant women with CHD and a history of tachyarrhythmias, arrhythmia recurrence or persistent tachyarrhythmia during pregnancy significantly worsens child outcome independently of other maternal cardiac risk factors [29]. Premature birth is the most common complication after maternal arrhythmia, followed by low birth weight, respiratory distress syndrome, intraventricular haemorrhage, and foetal death [29]. These foetal/neonatal events do not seem to be associated with a specific maternal arrhythmia type such as SVT, atrial fibrillation, or VT [29].

Risk factors for arrhythmias

Endeavouring to identify those specific patients with heart disease that are at risk for cardiac events during pregnancy, such as cardiac death, arrhythmias, heart failure, stroke, or myocardial infarction, the risk prediction models ZAHARA (*Zwangerschap bij Aangeboren Hartafwijking*) [5], CARPREG II (Cardiac Disease in Pregnancy Study II) [28, 30], and mWHO (modified World Health Organization classification) [9, 26] have been developed and optimised in the

last two decades. However, risk prediction models specifically for arrhythmias during pregnancy in patients with CHD are lacking. Tateno et al. examined factors predisposing to arrhythmias by comparing CHD patients with and without arrhythmias during pregnancy, and found an association of lower functional class and pre-existing heart failure with arrhythmia occurrence [32]. Consistent with this, increased N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels at 20 weeks' gestation and 1 year post-partum were identified as risk factor for arrhythmias post-partum [12].

A history of arrhythmia may also predispose to arrhythmias during pregnancy, as previous or pre-existing arrhythmia was reported in 20–50% of CHD patients experiencing arrhythmia during pregnancy [1, 29, 32]. A total of 31% of high-risk CHD patients with previous arrhythmias demonstrated renewed sustained arrhythmias during pregnancy, while in the group of high-risk CHD patients without a history of arrhythmia, no patient suffered sustained arrhythmia [25]. Specific maternal factors predisposing to arrhythmia recurrence during pregnancy could not be identified [29]. On the other hand, the occurrence of arrhythmias during pregnancy was associated with an increased risk for arrhythmias late post-partum in CHD patients [12].

Increasing CHD complexity has been associated with increased frequency of pregnancy-related cardiac events in general, and with arrhythmias specifically [1, 23]. Patients with complex CHD seem especially prone to serious ventricular arrhythmias, whereas occurrence of atrial rhythm disturbances is similar for both complex and simple CHD [10]. Closer inspection of those reports breaking down the numbers of arrhythmias into different CHD subtypes demonstrates that patients with simple CHD, e.g. shunt lesions or pulmonary valve stenosis, have a risk of under 5%, patients with moderately complex CHD, e.g. tetralogy of Fallot, approach a risk of 25%, and patients with highly complex CHD, e.g. single ventricle, have

Abstract · Zusammenfassung

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Abstract

Arrhythmias play a significant role in the morbidity and mortality of patients with adult congenital heart disease (CHD). Pregnancy-associated physiological changes in hormonal status, hemodynamics, and myocardial structure further enhance arrhythmic risk in CHD patients, leading to increased adverse maternal and foetal events and making arrhythmias one of the most common complications during pregnancy. Nearly all CHD patients are affected by asymptomatic rhythm disturbances during the ante-, peri-, or post-partum periods, and almost one tenth of patients develop sustained, symptomatic arrhythmias requiring treatment. The majority of arrhythmias originate from the atrium, mostly in the form of supraventricular tachycardia or atrial fibrillation. Patients with CHD often tolerate these even more poorly during pregnancy than before pregnancy. Sustained ventricular tachycardia or ventricular fibrillation are rare, but potentially life-threatening for mother and foetus. Risk stratification models developed specifically for arrhythmias during pregnancy in CHD patients are lacking, but direct or indirect signs of heart failure, previous history of arrhythmia, and complex CHD may be associated with higher arrhythmic risk in these patients. Rigorous individual assessment before, and careful monitoring during pregnancy in a multidisciplinary team is crucial to ensure the best possible pregnancy outcome for patients with CHD.

Keywords

Adult CHD · Arrhythmia · Obstetric status · Adverse maternal/foetal events · Risk prediction

Arrhythmierisiko in der Schwangerschaft bei Patientinnen mit angeborenem Herzfehler

Zusammenfassung

Arrhythmien haben einen signifikanten Einfluss auf die Morbidität und Mortalität erwachsener Patientinnen und Patienten mit angeborenen Herzfehlern (AHF). Physiologische Veränderungen des Hormonstatus, der Hämodynamik und der myokardialen Struktur während der Schwangerschaft steigern das Risiko für Herzrhythmusstörungen zusätzlich, sodass Arrhythmien eine der häufigsten Komplikationen während der Schwangerschaft darstellen und maternale und fetale Komplikationsraten signifikant erhöht sind. Fast alle Patientinnen mit AHF sind von asymptomatischen Herzrhythmusstörungen in der ante-, peri- oder postpartalen Phase betroffen, und etwa jede Zehnte erfährt symptomatische, anhaltende Arrhythmien, die einer Therapie bedürfen. Die meisten Arrhythmien gehen vom Vorhof aus, überwiegend als supraventrikuläre Tachykardie oder Vorhofflimmern. Diese atrialen Arrhythmien werden von Patientinnen mit AHF während der Schwangerschaft häufig noch schlechter toleriert als zuvor. Anhaltende ventrikuläre Tachykardien oder Kammerflimmern sind selten, jedoch potenziell lebensbedrohlich für Mutter und Fetus. Modelle zur Risikostratifizierung speziell für Arrhythmien in der Schwangerschaft bei Patientinnen mit AHF fehlen, es bestehen jedoch Hinweise, dass direkte und indirekte Zeichen der Herzinsuffizienz, vorangegangene Arrhythmien und komplexe AHF mit einem erhöhten Arrhythmierisiko bei diesen Patientinnen vergesellschaftet sind. Eine gründliche individuelle Evaluierung vor und ein sorgfältiges Monitoring während der Schwangerschaft in einem interdisziplinären Team sind unabdingbar, um einen bestmöglichen Schwangerschaftsverlauf für Patientinnen mit AHF zu ermöglichen.

Schlüsselwörter

Angeborene Herzfehler bei Erwachsenen · Herzrhythmusstörungen · Schwangerschaftsstatus · Maternale/fetale Komplikationen · Risikostratifizierung

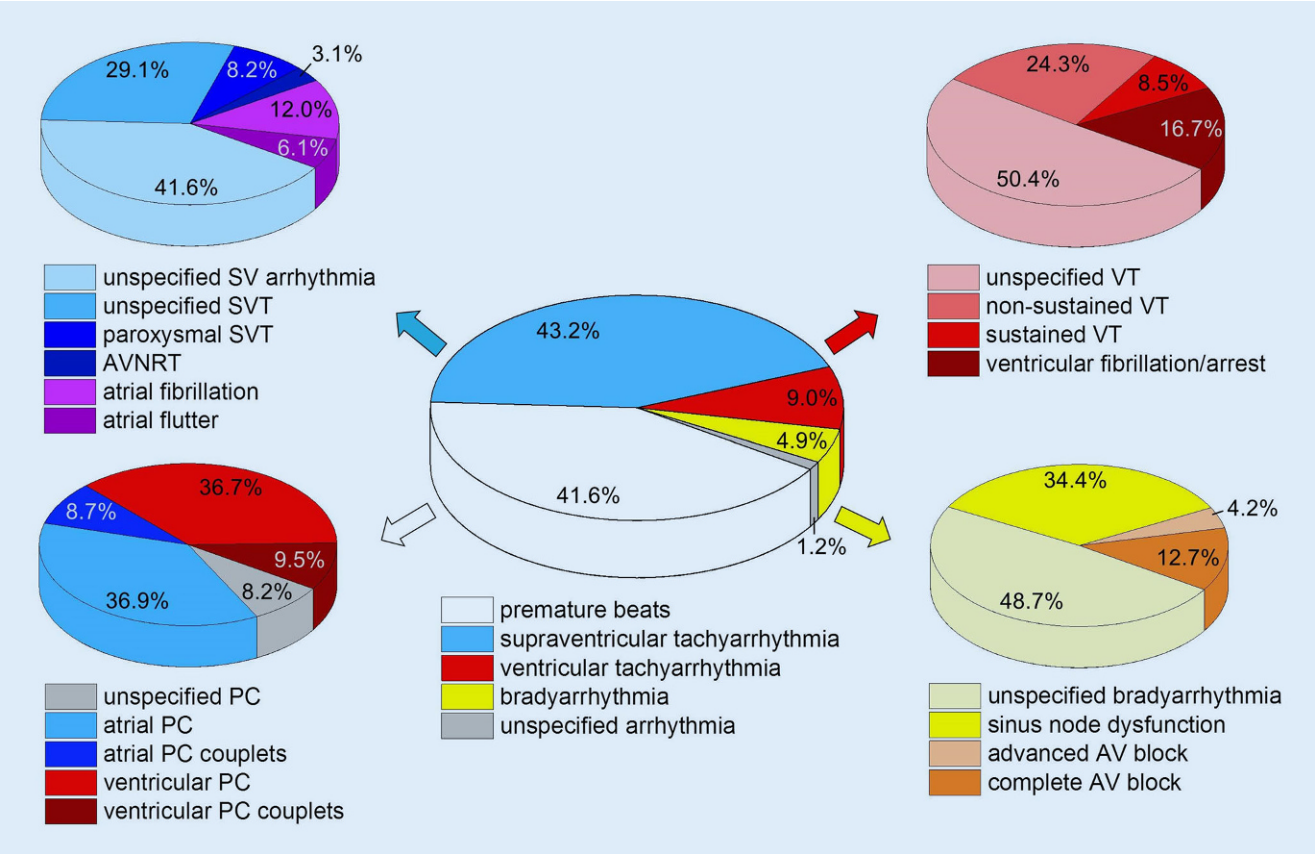

Fig. 1 ▲ Reported arrhythmia subtypes during pregnancy, delivery, and post-partum in patients with congenital heart disease. *Middle*: Percentages indicated in [12, 16, 22, 23, 30, 32] were weighted by cohort size and averaged to determine proportions of premature beats, supraventricular tachyarrhythmia, ventricular tachyarrhythmia, and bradyarrhythmia among all arrhythmia occurrences. From those studies that further specified arrhythmia type, arrhythmia categories were broken down into subtypes regarding supraventricular tachyarrhythmias (*top left*, data from [12, 16, 22, 23, 30, 32]), ventricular tachyarrhythmias (*top right*, data from [12, 16, 22, 23, 30, 32]), premature beats (*bottom left*, data from [12, 22, 23]), and bradyarrhythmias (*bottom right*, data from [22, 23, 30, 32]). *Red* indicates ventricular arrhythmias, *blue/purple* indicates atrial arrhythmias, and *yellow/orange* indicates bradyarrhythmias. *AV* atrioventricular, *AVNRT* atrioventricular node re-entry tachycardia, *SV* supraventricular, *SVT* supraventricular tachycardia, *PC* premature contractions, *VT* ventricular tachycardia

an over 30% risk of arrhythmias during pregnancy [5, 30].

Some CHD types inherently predispose to specific arrhythmia types, which may also present during pregnancy. For example, patients with tetralogy of Fallot are typically at risk for ventricular arrhythmias in the setting of long-standing pressure and/or volume overload, fibrosis, cellular remodelling, surgical scars, and patch material in the right outflow tract [8]. On the other hand, patients with simple transposition of the great arteries who have undergone the Mustard or Senning procedure are at increased risk for atrial re-entry tachycardia due to the extensive intra-atrial surgery, often complicated by a failing subaortic right ventricle [18]. Patients with single ventricle physiology are also affected by atrial arrhythmias, stemming from a combination of sinus node dysfunction, extensive atrial scarring, and myocardial remodelling [7]. Finally, atrial dilation and myocardial remodelling in advanced pulmonary arterial hypertension, especially Eisenmenger syndrome, also predispose to atrial arrhythmias [14]. As these atrial arrhythmias are often severely symptomatic, lead to hemodynamic instability, and are difficult to terminate, they pose a significant threat to mother and foetus when occurring during pregnancy [14, 18]. Indeed, patients with Eisenmenger syndrome bear the highest risk for adverse outcomes overall during pregnancy [24].

In summary, direct or indirect signs of heart failure, previous or pre-existing arrhythmias, and complexity of CHD may be indicative of enhanced risk for arrhythmias during pregnancy in CHD patients. One factor alone cannot account for arrhythmia predisposition during pregnancy, and when stratifying for arrhythmic risk in pregnant CHD patients these three components should be included in the assessment.

Management of arrhythmias during pregnancy

Arrhythmia management during pregnancy must be adapted to take into account potential teratogenicity of antiarrhythmic medication and procedures.

Data on drug therapy effectiveness for arrhythmias in pregnant CHD patients is sparse. Most anti-arrhythmic drugs have shown adverse foetal effects in animal models, but have not been studied in humans, or have not been studied in animals or humans at all [18, 26]. Therefore, anti-arrhythmic medication should only be used if potential benefits for the mother outweigh potential risks for the foetus, especially during the first trimester when teratogenic risk is highest. Meticulous ante-partum evaluation, including assessment for the need of anticoagulation, is called for to determine the best possible options for each individual patient. Detailed treatment recommendations can be found in the 2018 European Society of Cardiology (ESC) guidelines [26].

Practical conclusion

Arrhythmic complications during pregnancy in patients with CHD significantly influence both maternal and foetal outcome. While risk stratification models have been established for cardiac events in general during pregnancy, prediction of arrhythmia occurrence specifically in CHD patients remains under-investigated. Estimating arrhythmic risk requires thorough individual assessment of each patient regarding CHD complexity, previous history, and current cardiac and obstetric status to enable reliable counselling before, and adequate monitoring during, pregnancy. Early referral to a specialised, multidisciplinary adult CHD centre with experts not only in CHD and rhythmology, but also in obstetrics and neonatology, is key for successful planning and implementation of an individually tailored plan for pregnancy and delivery.

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Acknowledgements. The authors thank Prof. Peter Kohl and Dr. Eva Rog-Zielinska for their critical review of the manuscript.

Declarations

Conflict of interest. H.E. Fürniss and B. Stiller declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were performed in accordance with the ethical standards indicated in each case.

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