

STATE-OF-THE-ART PAPER

Outcome of Pregnancy in Women With Congenital Heart Disease

A Literature Review

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A search of peer-reviewed literature was conducted to identify reports that provide data on complications associated with pregnancy in women with structural congenital heart disease (CHD). This review describes the outcome of 2,491 pregnancies, including 377 miscarriages (15%) and 114 elective abortions (5%). Important cardiac complications were seen in 11% of the pregnancies. Obstetric complications do not appear to be more prevalent. In complex CHD, premature delivery rates are high, and more children are small for gestational age. The offspring mortality was high throughout the spectrum and was related to the relatively high rate of premature delivery and recurrence of CHD. (J Am Coll Cardiol 2007;49:2303-11) © 2007 by the American College of Cardiology Foundation

Progress in the fields of diagnostic techniques and surgical intervention has dramatically improved long-term outcome in congenital heart disease (CHD). As a consequence, most patients with congenital cardiac malformations reach child-bearing age, and many of these women wish to become pregnant. Pregnancy itself is a circulatory burden, primarily because of volume loading, which has a significant impact even on a healthy woman's life. In the face of residual lesions or sequelae after correction or an uncorrected maternal congenital heart defect, this burden may have deleterious effects on the health of both the mother and her offspring.

To provide an accurate and contemporary overview of the cardiac, obstetric, and neonatal complications during pregnancies in women with CHD, a literature review was conducted.

Methods

A systematic search of peer-reviewed literature using PubMed, MEDLINE, and the Cochrane Library databases was performed. Predefined limits were: 1) date of publication after January 1, 1985, for reasons of contemporaneous applicability; 2) the main body of text of the manuscript needed to be in English, German, or French to reduce misinterpretation; 3) the complications reported (in the methods or the results section) needed to be traceable to the patient's primary CHD; 4) the number of completed (not aborted or miscarried) pregnancies for the primary CHD category needed to be available; and 5) reviews and case reports describing ≤ 1 completed pregnancy were excluded. The search was performed separately by two independent researchers (W.D. and W.A.vL.).

For the present review, the baseline primary CHD and the number of completed pregnancies, miscarriages, and therapeutic abortions were recorded. In addition, the following complications were recorded for each completed pregnancy. *Cardiac complications:* reported clinically significant ("requiring treatment") episodes of arrhythmias (including origin and type of arrhythmia) or heart failure, cardiovascular events (myocardial infarction, cardiovascular mortality and/or cerebrovascular accidents), or endocarditis (including first 6 months postpartum). *Obstetric complications:* pregnancy-induced hypertension, preeclampsia, eclampsia,

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Abbreviations and Acronyms

AVSD = atrioventricular septal defect(s)

CHD = congenital heart disease

CoA = aortic coarctation

HELLP = hemolysis elevated liver enzymes low platelets

PAVSD = pulmonary atresia with ventricular septal defects

PS = pulmonary valve stenosis

SGA = small for gestational age

TGA = complete transposition of the great arteries

TOF = tetralogy of Fallot

hemolysis elevated liver enzymes low platelets (HELLP) syndrome, thromboembolic events (confirmed deep venous thrombosis or pulmonary embolus), premature rupture of membranes; premature labor (<37 weeks gestation), postpartum hemorrhage. *Offspring complications:* premature birth (delivery <37 weeks), small-for-gestational-age (SGA) birth weight (<10th percentile), fetal demise (intrauterine death \geq 20 weeks of gestation), and/or perinatal mortality (death within the first year of life).

The query consisted of: congenital heart disease (CHD, atrial septal defect, atrioventricular septal defect [AVSD], ventricular septal defect, aortic stenosis, aortic coarctation, pulmonary valve stenosis

[PS], pulmonary atresia, tetralogy of Fallot [TOF], transposition of the great arteries/vessels [TGA], Ebstein's, cyanotic heart disease, Eisenmenger, and Fontan) followed by: AND (pregnancy OR delivery). Abstracts of the identified articles were read on the basis of this information and the eligible articles were identified. Subsequently, full-text papers were ordered or downloaded. If a report could not be ordered through our library, attempts were made to contact the authors. Additional reports were found through cross-reading the reference lists of the eligible articles. The available reports were independently read by 2 researchers (Dr. Drenthen and Dr. van Lottum) and classified according to the defined criteria. When discrepancies between the 2 researchers were discovered, a third independent adult congenital cardiologist was asked to interpret the data. This third party then decided how the data should be interpreted. Efforts were made to filter out duplicates; publications from the same institution were checked for the period of data collection. The format of the review was structured and analyses were performed according to the Cochrane guidelines.

Results

The literature search was performed between November 1, 2005, and October 1, 2006. Searching the Cochrane Library database, we found no reviews. Systematic literature search of PubMed and MEDLINE retrieved 48 different, mainly retrospective, publications describing 2,491 pregnancies, including 377 miscarriages (15%) and 114 (5%) elective abortions (1-48). It proved impossible to subdivide complications based on surgical status before pregnancy for every CHD category separately. Patients with TGA had undergone atrial correction before pregnancy, except for 3 arterial switch patients. All patients with TOF had under-

gone definitive repair. All pulmonary atresia with ventricular septal defects (PAVSD) patients had received biventricular repair. The remaining uncorrected or palliated TGA, TOF, and PAVSD patients were incorporated in the category (palliated or uncorrected) of cyanotic heart disease. The other CHD cohorts contained a mix of corrected and uncorrected patients.

Figure 1 provides an overview of the distribution of gestations (completed, miscarriage, and elective abortions) per CHD. Figure 2 shows the occurrence of the most important cardiac, obstetric, and offspring complications recorded in the reviewed literature during completed (not aborted or miscarried) pregnancies organized per CHD. Tables 1 through 3 provide detailed information on each complication.

The most frequently encountered cardiac complication (Table 1) was clinically significant heart failure (4.8%). Patients with complex CHD (Eisenmenger, other cyanotic heart disease, and PAVSD) appeared to be at special risk. Arrhythmias complicated 70 (4.5%) of the completed pregnancies. Most of the arrhythmias were supraventricular tachyarrhythmias (n = 48). Ventricular tachyarrhythmias were reported in 9 patients, bradyarrhythmias in 3 patients, and Wolff-Parkinson-White syndrome in 1 patient; in 9 pregnancies the exact nature of the arrhythmia was not reported. Cardiovascular events (myocardial infarction, stroke, and cardiovascular mortality) were documented primarily in Eisenmenger patients and those with palliated or uncorrected cyanotic heart disease.

Obstetric complications (Table 2) were less well documented. In general, hypertensive disorders related to pregnancy do not appear to be more prevalent for the whole CHD cohort. Eclampsia and HELLP syndrome were reported in 3 (PS [n = 2] and PAVSD [n = 1]) and 2 (PAVSD and TGA), respectively, of the 904 completed pregnancies (not depicted in Table 2). Especially noteworthy, the incidence of preeclampsia and eclampsia in patients with TGA, PS, aortic coarctation, and PAVSD exceeded the expected rate of 2% to 3%. Thromboembolic events, predominantly pulmonary embolisms, were observed in approximately 2% of the pregnancies.

Fetal complications (Table 3) were incorporated more frequently in the methodology of the reviewed articles. Importantly, overall offspring mortality was 4%, which could at least in part be attributed to the relatively high overall premature birth rate (16%) and the recurrence of CHD. The recurrence rate depended on the type of CHD and ranged between 0.6% (TGA) and 8% (AVSD).

Discussion

The present systematic review described the outcome of 2,491 pregnancies in women with different types of CHD. Most pregnancies were successful, though complications were observed. Arrhythmias, heart failure, and cardiovascular events, rarely seen in the healthy general population,

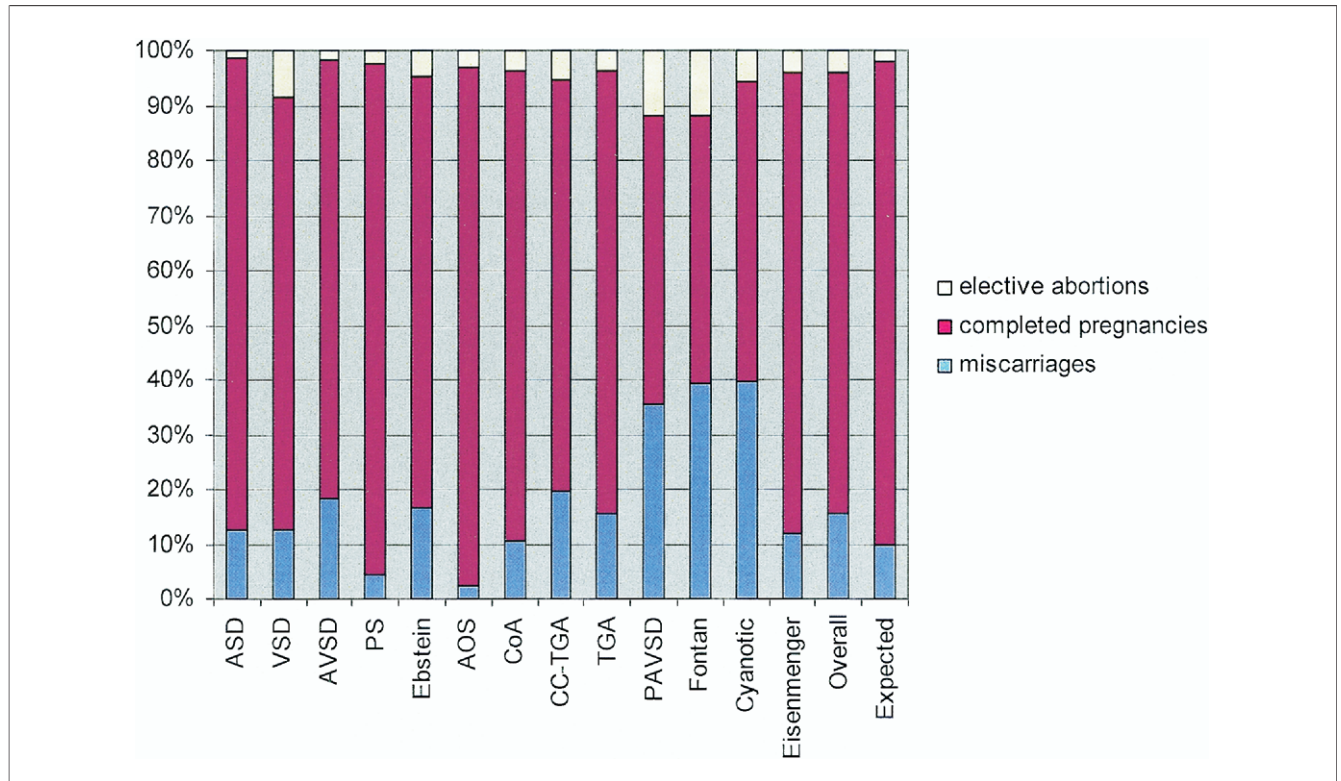


Figure 1 Pregnancy Outcome in Women With Congenital Heart Disease

Distribution of miscarriages, completed pregnancies, and elective abortions for each congenital heart disease are shown separately and as overall rates. On the **right side**, the expected rates in healthy women are depicted. AOS = aortic stenosis; ASD = atrial septal defect; AVSD = atrioventricular septal defects; CC-TGA = congenital corrected transposition of the great arteries; CoA = aortic coarctation; Ebstein = Ebstein's anomaly; Eisenmenger = Eisenmenger syndrome; Fontan = patients after Fontan repair; PAVSD = pulmonary atresia with ventricular septal defects; PS = pulmonary valve stenosis; TGA = complete transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

were documented during 11% of completed pregnancies. Obstetric complications, on the other hand, did not appear to be more prevalent, except for hypertensive disorders and thromboembolic events. Offspring mortality was high (4% vs. <1% in the general population), and occurred particularly in CHD cohorts with high rates of premature delivery and/or recurrence of CHD.

Supraventricular and ventricular arrhythmias requiring treatment are rarely seen during pregnancy in healthy women (49,50). Potential factors that promote the development of arrhythmias are the additional circulatory burden of pregnancy and local electrophysiologic effects, more specifically the extra volume load and the enhanced adrenergic receptor excitability mediated by estrogens and progesterone (51,52). Structural cardiac defects or residual defects after repair may contribute to the occurrence of clinically relevant arrhythmias. Most recorded arrhythmias were supraventricular in origin. In particular, patients with TGA, Fontan repair, and atrioventricular septal defects appeared at risk. Surgical scar tissue formation may play a role in the pathophysiologic mechanism. In the TGA population, most patients had undergone atrial repair (Mustard or Senning) with baffle formation. Patients after Fontan repair, especially after atriopulmonary anastomosis and

atrioventricular connection, were at risk for atrial tachyarrhythmias owing to the exposure of right atrial tissue to higher than normal pressures. In patients with AVSD, macro-re-entrant tachycardias are well-known complications after repair and, in addition, (residual) left atrioventricular regurgitation may play a role in the development of arrhythmias.

In the healthy general population, heart failure needing medical intervention is uncommon and mainly related to the development of peripartum cardiomyopathy (53). In our review, patients with complex CHD (in particular, patients with cyanotic heart disease, Eisenmenger syndrome, and PAVSD) appeared prone to develop heart failure. Overall, clinically significant ("needing medical intervention") heart failure was observed in almost 5% of the completed pregnancies. Most episodes resolved without sequelae using medication. It needs to be said, however, that the given heart failure rate may be an underestimation, considering that early heart failure was an important reason for elective abortion.

Cardiovascular events (myocardial infarction, cerebrovascular accidents, and mortality) are observed during 1 of every 50 pregnancies. Mortality was particularly high in patients with Eisenmenger syndrome. Therefore, we still

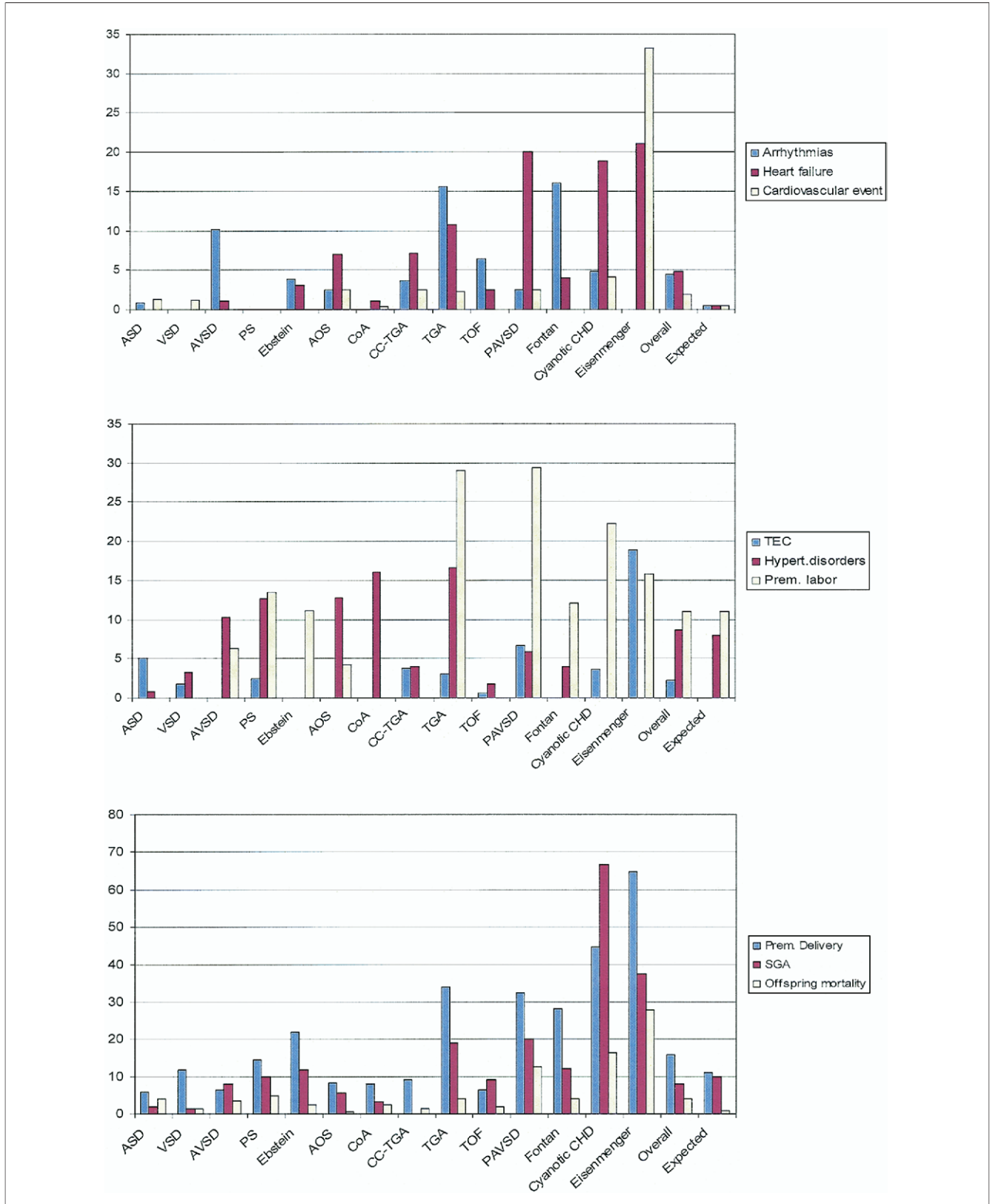


Figure 2 Distribution of Complications During Pregnancy in Women With CHD

Overview of the most important complications encountered during pregnancy in women with structural congenital heart disease (CHD) for each CHD separately and the overall rates. On the **right side**, the expected rates in healthy women are depicted. SGA = small for gestational age; TEC = thromboembolic complications; other abbreviations as in [Figure 1](#).

Table 1 Overview of Cardiac Complications Encountered During Completed (>20 Weeks Gestation) Pregnancies Summarized and Sorted by Maternal Primary Cardiac Diagnosis for Articles Published Between 1985 and 2006*

Congenital Heart Disease (Ref. no.)	Arrhythmias		Heart Failure		Cardiovascular Events		Endocarditis	
	Events, n (%)	Pregnancies, n	Events, n (%)	Pregnancies, n	Events, n (%)	Pregnancies, n	Events, n (%)	Pregnancies, n
ASD (1,20,27,33,45)	1 (0.8)	123	0 (0.0)	132	2 (1.3)	149	1 (3.8)	26
VSD (20,27,33,45)	0 (0.0)	66	0 (0.0)	74	1 (1.2)	83	0 (0.0)	17
AVSD (13,45)	9 (10.2)	88	1 (1.1)	88	0 (0.0)	88	0 (0.0)	48
PS (17,27,33,35,36,48)	0 (0.0)	100	0 (0.0)	110	0 (0.0)	123	0 (0.0)	102
Ebstein (9,10,20,27,35,36)	5 (3.9)	127	4 (3.1)	127	0 (0.0)	128	0 (0.0)	127
AOS (14,17,20,21,27,28,33–36)	4 (2.4)	168	14 (7.0)	200	5 (2.5)	200	1 (0.6)	175
CoA (3,20,27,29,32,33,35,36,41–44)	0 (0.0)	297	3 (1.0)	303	1 (0.3)	304	0 (0.0)	303
CC-TGA (8,20,36,39)	3 (3.6)	84	6 (7.1)	84	2 (2.4)	84	1 (1.2)	84
TGA (6,12,15,16,20,22–24,27,33,35,36,47)	27 (15.6)	173	19 (10.8)	176	4 (2.2)	178	0 (0.0)	178
TOF (20,25,27,33,35,36,40,45)	13 (6.4)	204	5 (2.4)	211	0 (0.0)	222	1 (0.6)	174
PAVSD (7,26,46)	1 (2.5)	40	8 (20.0)	40	1 (2.5)	40	0 (0.0)	40
Fontan (4,5,11,18)	4 (16.0)	25	1 (4.0)	25	0 (0.0)	25	0 (0.0)	25
Cyanotic CHD (30,31,33,35)	3 (4.8)	63	14 (18.9)	74	3 (4.1)	74	3 (4.1)	74
Eisenmenger (2,19,27,29,37,38,44)	0 (0.0)	4	4 (21.1)	19	14 (33.3)	42	0 (0.0)	2
Overall	70 (4.5)	1,562	79 (4.8)	1,663	33 (1.9)	1,740	7 (0.5)	1,372
Expected occurrence (%)	<0.5		<0.5		<0.5		<0.01	

*Expressed as number of complications/completed pregnancy (percentage per completed pregnancy).

AOS = aortic stenosis; ASD = atrial septal defect; AVSD = atrioventricular septal defects; CC-TGA = congenital corrected transposition of the great arteries; CHD = congenital heart disease; CoA = aortic coarctation; Ebstein = Ebstein's anomaly; Eisenmenger = Eisenmenger syndrome; Fontan = patients after Fontan repair; PAVSD = pulmonary atresia with ventricular septal defects; PS = pulmonary valve stenosis; TGA = complete transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

advocate that pregnancy should be discouraged in these patients. It needs to be taken into account, however, that mortality is likely to be underestimated, as most research is performed in retrospective or so-called survivor cohorts. Therefore, we have not described mortality as a separate complication. For accurate estimations of serious and relatively rare complications a large-scale (multicenter and international) prospective registration remains necessary.

With regard to the occurrence of endocarditis, it is striking that patients with simple secundum atrial septal defect appear to be at greater risk. Details on the site of infection, the causative organism, and circumstances including the presence of concomitant minor (anatomic or physiologic) abnormalities that may increase the risk of endocarditis are not described. This area needs to be further investigated.

Pregnancy-related hypertensive disorders were documented in 8.7% of the pregnancies, which is comparable to the 8% found in the general population (54). In four CHD categories, however, the incidence of hypertensive disorders appears substantially higher. In patients with aortic stenosis, PS, aortic coarctation, and TGA, hypertensive disorders occurred in respectively 12.8%, 14.3%, 16.0%, and 16.3% of completed pregnancies. Preeclampsia is a relatively rare condition with a reported incidence in the developed countries between 2% and 3%; eclampsia is even rarer, with estimated incidences of 4 to 5 cases per 10,000 live births. Both entities are generally associated with substantial maternal and neonatal morbidity (55,56). Preeclampsia appeared to cluster in patients with aortic coarctation, PS, PAVSD, and TGA. Several mechanisms, either solitary or

combined, may be hypothesized. First, activation of neuro-hormonal pathways in patients with CHD may alter vascular remodeling associated with pregnancy-induced hypertension and (pre-)eclampsia. Second, endothelial dysfunction is present in patients with CHD. Finally, oxidative stress may interact with the pathophysiologic mechanisms behind pregnancy-induced hypertension and (pre-)eclampsia.

During pregnancy and the postpartum period, patients are at risk for thromboembolic complications owing to the presence of all three components of Virchow's triad: venous stasis, endothelial injury, and a hypercoagulable state. Nevertheless, thromboembolic events are normally seen only once per 1,000 to 2,000 pregnancies (57,58). Fifteen thromboembolic complications occurred, which suggests that the incidence in women with CHD (1:50) is substantially increased compared with the general population. Importantly, associated disorders, such as the presence of inherited thrombophilia, malignancy, systemic disease, recent surgery or trauma, disease needing hormonal replacement therapy, or bone marrow diseases, were insufficiently documented. This finding merits further investigation.

Premature birth rate (16%) also appeared higher than generally reported in the industrialized world (10% to 12%). In patients with more complex CHD, including Ebstein, TGA, PAVSD, Fontan, cyanotic CHD, and Eisenmenger, the preterm delivering rates ranged between 22% and 65%. Premature labor seems to play an important role in the higher incidence of premature birth in these CHD categories. Several premature deliveries were iatrogenic, which may imply a greater tendency of the attending gynecologist

Table 2 Overview of Pregnancy/Obstetric Complications Encountered During Completed (>20 Weeks Gestation) Pregnancies Summarized and Sorted by Maternal Primary Cardiac Diagnosis for Articles Published Between 1985 and 2006*

Congenital Heart Disease (Ref. no.)	PIH		Preeclampsia		TEC		PROM		Premature Labor		PPH	
	Events, n (%)	Pregnancies, n	Events, n (%)	Pregnancies, n	Events, n (%)	Pregnancies, n	Events, n (%)	Pregnancies, n	Events, n (%)	Pregnancies, n	Events, n (%)	Pregnancies, n
ASD (1,20,27,33,45)	0 (0.0)	93	3 (0.8)	248	1 (5.0)	20	NA	NA	NA	NA	0 (0.0)	9
VSD (20,27,33,45)	1 (1.5)	65	1 (1.8)	57	1 (1.8)	57	NA	NA	NA	NA	0 (0.0)	8
AVSD (13,45)	7 (8.0)	88	2 (2.3)	88	0 (0.0)	88	0 (0.0)	48	3 (6.3)	48	10 (20.8)	48
PS (17,27,33,35,36,48)	7 (7.7)	91	4 (4.9)	81	2 (2.5)	81	5 (6.2)	81	11 (13.5)	81	13 (14.3)	91
Ebstein (9,10,20,27,35,36)	NA	NA	NA	NA	NA	NA	NA	NA	4 (11.1)	36	NA	NA
AOS (14,17,20,21,27,28,33-36)	5 (12.8)	39	0 (0.0)	20	0 (0.0)	20	0 (0.0)	20	1 (4.2)	24	1 (2.2)	45
CoA (3,20,27,29,32,33,35,36,41-43)	27 (11.1)	244	12 (4.9)	245	0 (0.0)	33	0 (0.0)	132	0 (0.0)	132	0 (0.0)	139
CC-TGA (8,20,36,39)	1 (2.0)	50	1 (2.0)	50	1 (3.7)	27	NA	NA	NA	NA	NA	NA
TGA (6,12,15,16,20,22-24,27,33,35,36,47)	5 (8.3)	80	8 (10.3)	78	2 (3.0)	66	10 (17.5)	57	18 (29.0)	62	9 (13.8)	65
TOF (20,25,27,33,35,36,40,45)	0 (0.0)	176	3 (1.8)	169	1 (0.6)	169	1 (0.8)	132	NA	NA	5 (8.8)	57
PAVSD (7,26,46)	0 (0.0)	17	1 (5.9)	17	2 (6.7)	30	0 (0.0)	7	5 (29.4)	17	0 (0.0)	7
Fontan (4,5,11,18)	1 (4.0)	25	0 (0.0)	25	0 (0.0)	25	4 (16.0)	25	3 (12.0)	25	2 (8.0)	25
Cyanotic CHD (30,31,33,35)	0 (0.0)	21	0 (0.0)	9	2 (3.6)	56	0 (0.0)	9	2 (22.2)	9	2 (9.5)	21
Eisenmenger (2,19,27,29,37,38,44)	NA	NA	0 (0.0)	11	3 (18.8)	16	0 (0.0)	1	3 (15.8)	19	2 (28.6)	7
Overall	54 (5.5)	989	35 (3.2)	1,098	15 (2.2)	688	20 (3.9)	512	50 (11.0)	453	44 (8.4)	522
Expected occurrence (%)	5.0		2.0-3.0		0.1		3.5		10.0-12.0		Not known	

*Expressed as number of complications/completed pregnancy (percentage per completed pregnancy).

PIH = pregnancy-induced hypertension; PPH = postpartum hemorrhage; PROM = premature rupture of membranes; TEC = thromboembolic complications; other abbreviations as in Table 1.

Table 3 Overview of Offspring Complications Encountered During Completed (>20 Weeks Gestation) Pregnancies Summarized and Sorted by Primary Maternal Cardiac Diagnosis for Articles Published Between 1985 and 2006*

Congenital Heart Disease (Ref. no.)	Premature Delivery		SGA		Fetal Mortality		Perinatal Mortality		CHD Recurrence	
	Events, n (%)	Pregnancies, n	Events, n (%)	Pregnancies, n	Events, n (%)	Pregnancies, n	Events, n (%)	Pregnancies, n	Events, n (%)	Pregnancies, n
ASD (1,20,27,33,45)	10 (6.0)	168	5 (1.8)	274	7 (2.4)	291	5 (1.7)	291	6 (2.1)	291
VSD (20,27,33,45)	2 (11.8)	17	1 (1.4)	74	1 (1.4)	74	0 (0.0)	74	2 (2.7)	74
AVSD (13,45)	3 (6.3)	48	7 (8.0)	88	1 (1.1)	88	2 (2.3)	88	7 (8.0)	88
PS (17,27,33,35,36,48)	16 (14.5)	110	11 (10.0)	110	1 (0.8)	123	5 (4.1)	123	3 (2.8)	104
Ebstein (9,10,20,27,35,36)	28 (22.0)	127	5 (11.9)	42	0 (0.0)	128	3 (2.3)	128	5 (4.0)	126
AOS (14,17,20,21,27,28,33-36)	12 (8.3)	145	8 (5.5)	145	0 (0.0)	158	1 (0.6)	158	5 (4.1)	121
CoA (3,20,27,29,32,33,35,36,41-43)	20 (7.9)	253	7 (3.1)	224	0 (0.0)	254	6 (2.4)	254	10 (4.0)	251
CC-TGA (8,20,36,39)	7 (9.0)	78	0 (0.0)	28	1 (1.3)	78	0 (0.0)	78	1 (3.6)	28
TGA (6,12,15,16,20,22-24,27,33,35,36,47)	43 (34.1)	126	18 (19.0)	95	5 (2.8)	179	2 (1.1)	179	1 (0.6)	176
TOF (20,25,27,33,35,38,40,45)	11 (6.3)	174	19 (9.0)	211	1 (0.5)	222	3 (1.4)	222	6 (3.0)	202
PAVSD (7,26,46)	13 (32.5)	40	6 (20.0)	30	1 (2.5)	40	4 (10.0)	40	3 (7.5)	40
Fontan (4,5,11,18)	7 (28.0)	25	3 (12.0)	25	0 (0.0)	25	1 (4.0)	25	1 (4.0)	25
Cyanotic CHD (30,31,33-35)	33 (44.6)	74	18 (66.7)	27	9 (12.2)	74	3 (4.1)	74	5 (7.4)	68
Eisenmenger (2,19,27,29,37,38,44)	22 (64.7)	34	3 (37.5)	8	4 (9.5)	42	4 (18.2)	22	1 (5.0)	20
Overall	224 (15.9)	1,413	110 (8.0)	1,381	31 (1.7)	1,776	41 (2.3)	1,756	56 (3.5)	1,616
Expected occurrence (%)	10.0-12.0		10.0		<0.5		<0.5		NA	

*Expressed as number of complications/completed pregnancy (percentage per completed pregnancy).
 SGA = small for gestational age; other abbreviations as in Table 1.

to intervene in women with CHD. A high incidence of premature rupture of membranes may have played a role in patients with TGA and Fontan. Spontaneous premature deliveries occurred frequently before 34 weeks of gestation, which has important clinical repercussions.

Small-for-gestational-age children were documented in the same types of CHD as premature delivery, except for patients with Fontan repair. In Fontan, premature deliveries could be attributed mainly to the excessive occurrence of premature rupture of membranes. In the other types of CHD, a similar pathophysiologic mechanism may explain the higher incidence of premature delivery, as well as the SGA children. In both complications, placental insufficiency plays a pivotal role. Investigation of the fetal-placental circulation in these women is necessary.

An important finding of the present systematic review is that children of women with CHD are at higher risk for fetal and perinatal mortality. In the industrialized world, fetal and perinatal mortality is below 1%. Therefore, the chance of offspring mortality is on average increased by 4 times. Importantly, in the types of CHD with high rates of premature delivery and/or CHD recurrence, this risk was more profound, ranging up to 27.7% in women with Eisenmenger syndrome. The recurrence risks are in agreement with the larger genetic cohort studies.

Several limitations of the present systematic review need to be discussed. The quality of the review depends on the design of the articles included. The study designs ranged from prospectively included cohort studies to case series reporting 2 completed pregnancies; therefore, the results need to be judged with caution. Moreover, publication bias is an important factor, especially in case series. Selection bias is introduced by excluding articles based on earlier-mentioned criteria. Underreporting of complications may also be an important problem.

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