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Frequency of Miscarriage/Stillbirth and Terminations of Pregnancy Among Women With Congenital Heart Disease in Germany, Hungary and Japan

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Background: The 2011 guidelines of the European Society of Cardiology (ESC) on the management of cardiovascular diseases during pregnancy define the maternal predictors for neonatal complications. The aim of this study was to determine whether these are associated with an increased number of miscarriages/stillbirths and terminations of pregnancy (TOPs) also in patients with congenital heart defects (CHD).

Methods and Results: The 634 women from Germany, Hungary and Japan were surveyed concerning the issues of sexuality and reproductive health, as well as their general life situation and medical care. 25% of the recorded pregnancies in women with CHD resulted in miscarriage, stillbirth or TOP. Affecting 16.8% of all recorded pregnancies, miscarriages or stillbirths occurred more frequently than in the general population and more than previously recorded for patients with CHD. TOP occurred in 8% of the surveyed pregnancies. Underlying maternal predictors for neonatal events had an influence on the number of TOP; among those with underlying predictors, TOP was recorded 3-fold more than in those without such predictors (15.6% vs. 5.5%). Remarkably, a significant deficit regarding the level of information on potential pregnancy-associated risks was observed in all 3 participating countries.

Conclusions: Pregnant women with CHD should always be treated and counseled individually by cardiologists, gynecologists, obstetricians and anesthetists with appropriate expert knowledge. (*Circ J* 2016; **80:** 1846–1851)

Key Words: Adult congenital heart disease; Miscarriage; Neonatal complications; Pregnancy; Stillbirth

More and more patients with congenital heart defects (CHD) have reached adulthood in the past decades. In contrast to 50 years ago when only 20–30% of all children with CHD survived into adulthood, this applies to over 90% of those affected today, thanks to improvements in diagnosis and treatment.[1] Enjoying an increased quality of life, affected women often express a desire for starting a family including their own children despite possible cardiac complications caused by the hemodynamic changes associated with pregnancy.[2–4]

The 2011 guidelines of the European Society of Cardiology (ESC) on the management of cardiovascular diseases during pregnancy define predictors (NYHA class >II before onset of pregnancy, maternal left heart obstruction, smoking during pregnancy, multiple pregnancy, taking oral anticoagulants during pregnancy, mechanical heart valve) for the occurrence of neonatal complications such as preterm delivery, low birth weight, miscarriage or perinatal mortality, infant respiratory

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Table 1. Baseline Characteristics of Participants in a Study of Pregnant Women With Congenital Heart Diseases in 3 Countries

	Germany n=390 (61%)	Hungary n=153 (24%)	Japan n=91 (15%)	Total n=634
Age (years)				
Median	30	29	31	30
Mean value (SD)	32.1 (±10.0)	33.0 (±12.9)	32.7 (±9.9)	32.4 (±10.8)
Minimum	18	18	19	18
Maximum	84	76	72	84
Severity of CHD*				
Simple	108 (27.7%)	96 (62.7%)	38 (41.8%)	242 (38.2%)
Moderate	179 (45.9%)	42 (27.5%)	38 (41.8%)	259 (40.9%)
Severe	103 (26.4%)	15 (9.8%)	15 (16.5%)	133 (21.0%)
Functional class**				
I+II	361 (92.6%)	151 (98.7%)	88 (96.7%)	600 (94.6%)
III+IV	29 (7.4%)	2 (1.3%)	3 (3.3%)	34 (5.4%)
Diagnosis				
Post-tricuspid shunts	49 (12.6%)	19 (12.4%)	27 (29.7%)	95 (15.0%)
Pre-tricuspid shunts	59 (15.1%)	59 (38.6%)	11 (12.1%)	129 (20.3%)
Left heart obstructions	67 (17.2%)	35 (22.9%)	10 (11.0%)	112 (17.7%)
Right heart obstructions	85 (21.8%)	20 (13.1%)	20 (22.0%)	125 (19.7%)
Complex anomalies	70 (17.9%)	12 (7.8%)	12 (13.2%)	94 (14.8%)
Marfan's syndrome	22 (5.6%)	3 (2.0%)	1 (1.1%)	26 (4.1%)
Cardiomyopathies (familial)	5 (1.3%)	0 (0%)	2 (2.2%)	7 (1.1%)
Other	33 (8.5%)	5 (3.3%)	8 (8.8%)	46 (7.3%)
Cyanosis/Eisenmenger syndrome				
Cyanosis	36 (9.2%)	3 (2.0%)	4 (4.4%)	43 (6.8%)
Eisenmenger syndrome	16 (4.1%)	2 (1.3%)	2 (2.2%)	20 (3.2%)
Received treatment				
Native CHD	90 (23.4%)	30 (19.6%)	22 (24.2%)	142 (22.6%)
Palliative surgery	35 (9.1%)	5 (3.3%)	6 (6.6%)	46 (7.3%)
Reparative surgery	233 (60.7%)	76 (49.7%)	62 (68.1%)	371 (59.1%)
Intervention	26 (6.8%)	42 (27.5%)	1 (1.1%)	69 (11.0%)
Missing values	6	0	0	6
Implants				
Valve replacement or conduit	38 (9.7%)	11 (7.2%)	6 (6.6%)	55 (8.7%)
Pacemaker implantation	29 (7.4%)	0	2 (2.2%)	31 (4.9%)
ICD implantation	8 (2.1%)	3 (2.0%)	0	11 (1.7%)
Arterial hypertension				
No hypertension	343 (88.4%)	129 (84.3%)	87 (95.6%)	559 (88.4%)
Mild hypertension	20 (5.2%)	5 (3.3%)	1 (1.1%)	26 (4.1%)
Moderate hypertension	2 (0.5%)	0	0	2 (0.3%)
Antihypertensive therapy	23 (5.9%)	19 (12.4%)	3 (3.3%)	45 (7.1%)
Missing values	2	0	0	2
History of infective endocarditis	11 (2.8%)	0	7 (7.7%)	18 (2.6%)
History of thromboembolism***	34 (8.8%)	17 (11.2%)	5 (5.5%)	56 (8.8%)
History of heart failure	31 (7.9%)	3 (2.0%)	11 (12.1%)	45 (7.1%)

*According to the American College of Cardiology;[11] **according to Perloff et al;[10] ***includes patients with at least one of the following diagnoses: phlebothrombosis, pulmonary embolism, TIA/PRIND/cerebral insult, peripheral arterial embolism. CHD, congenital heart defects; ICD, implantable cardioverter-defibrillator; PRIND, prolonged reversible ischemic neurologic deficit; TIA, transient ischemic attack.

distress syndrome and cerebral hemorrhage.[5–8] It is unknown whether these predictors are associated with an increased number of miscarriages/stillbirths also in patients with CHD.

The aim of the present study was to investigate the course of pregnancies in women with CHD in connection with maternal predictors for neonatal complications.

In addition, potential differences among the participating countries were examined in view of existing cultural and socioeconomic divergences.

Methods

In this multicenter study, 634 women with CHD arriving by ambulance at the participating hospitals during the observa-

Table 2. Overview of Pregnancies and Underlying Maternal Predictors for Neonatal Complications Among the Participants in a Study of Pregnant Women With Congenital Heart Diseases

	Germany (n=390)	Hungary (n=153)	Japan (n=91)	Total (n=634)
Pregnant at least once				
Yes	187 (47.9%)	71 (46.4%)	51 (56.0%)	309 (48.7%)
No	203 (52.1%)	82 (53.6%)	40 (44.0%)	325 (51.3%)
Age at first pregnancy (years)				
Median	26	23	27	26
Mean value (SD)	25.9 (±4.8)	24.0 (±4.9)	26.7 (±4.8)	25.6 (±4.9)
Minimum	15	17	16	15
Maximum	42	38	34	42
Missing values	14	4	2	20
Underlying maternal predictors for neonatal complications				
Yes	136 (34.9%)	26 (17.0%)	20 (22.0%)	182 (28.7%)
No	254 (65.1%)	127 (83.0%)	71 (78.0%)	452 (71.3%)

tion period and consenting to participation were included.

The participating centers for adult congenital heart disease (ACHD) were located in Germany (German Heart Centre Munich, German Heart Institute Berlin), Hungary (Gottsegen Hungarian Institute of Cardiology, Pediatric Cardiac Centre, Budapest; University of Szeged, Faculty of Medicine, Szeged) and Japan (Chiba Cardiovascular Centre, Ichihara).

Patients were surveyed concerning issues of sexuality and reproductive health, as well as their general life situation and medical care, via a 45-item questionnaire.

In addition, a questionnaire addressed to each attending physicians was used to record the cardiac diagnosis, previous surgery and catheter-based interventions, the clinical state and the current cardiac medication.

The study was approved by all the ethics committees of the participating centers.

Statistical Analysis

For statistical analysis, SPSS, version 19 (SPSS Inc, IBM) was used. In the descriptive analysis, metric variables are given as mean value or median, while nominal and ordinal-scaled data are given as frequency and per cent. The Kolmogorov-Smirnov test was used for testing for normal distribution. In the case of normal distribution, differences between groups were tested for significance by means of the Student's t-test, or, if there were more than 2 groups, by means of variance analysis. In the case of non-normal distribution, the Mann-Whitney U test and the Kruskal-Wallis test were used. The level of significance was set at 0.05, as customary.[9]

For data analysis, the study participants were grouped into 8 diagnosis groups according to their primary cardiac diagnosis (native CHD). In addition, they were assigned to different groups depending on their functional class, the severity of their CHD and underlying predictors for neonatal complications.

The functional classes (FC) were defined according to Perloff et al.[10] FC I and II, as well as III and IV, were combined into 1 group each for evaluation. For the classification of disease severity, the recommendations of the American College of Cardiology were used in modified form. According to these recommendations, simple CHD can be defined as those who can usually be cared for by the general medical community; patients with moderate CHD should be seen periodically at regional ACHD centers; and patients with severe CHD are those who should be seen regularly at such centers.[11]

In the questionnaire, miscarriages and stillbirths were combined, which is why they were also combined for analysis.

Results

Medical Patients Characteristics

Of the 634 patients, 61.5% (n=390) were from Germany, 24.1% (n=153) from Hungary and 14.4% (n=91) from Japan. The median age of all patients was 30 years (mean value: 32.4 years, SD: 10.8 years; range: 18–84 years). No significant differences were found between Germany, Hungary and Japan regarding age. In all 3 participating countries, half of the surveyed patients were between 18 and 29 years old (Germany: 44.1%, Hungary: 50.3%, Japan: 47.3%); 80% of the total study population were younger than 40 years at the time of the survey. Table 1 provides an overview of the clinical characteristics of the study population.

Pregnancies

At the time of the survey, 48.7% of the study participants had been pregnant at least once (Germany: 47.9% [n=187]; Hungary: 46.4% [n=71]; Japan: 56.0% [n=51]), and 26.9% (n=83) were currently pregnant.

The participants' median age at the time of the first pregnancy was 26 years (mean value: 25.6 years, SD: 4.9 years). At the time of the first pregnancy, the patients from Hungary were significantly younger than those from Germany (P=0.006) and Japan (P=0.003). No significant difference was found between the study participants from Germany and Japan regarding their age at the time of the first pregnancy.

Of the 309 women who had been pregnant at least once, 74.4% (n=230) stated having children of their own. The average number of children was 1.53 children per woman. Regarding this issue, there was no significant difference between Germany, Hungary and Japan. An overview of the pregnancies is given in Table 2.

Miscarriages, Stillbirths and Terminations of Pregnancy (TOP)

In 309 women, a total of 578 pregnancies had occurred (Germany: n=338, Hungary: n=134, Japan: n=106). A comparison of the 3 participating countries revealed no significant difference regarding the number of pregnancies per patient.

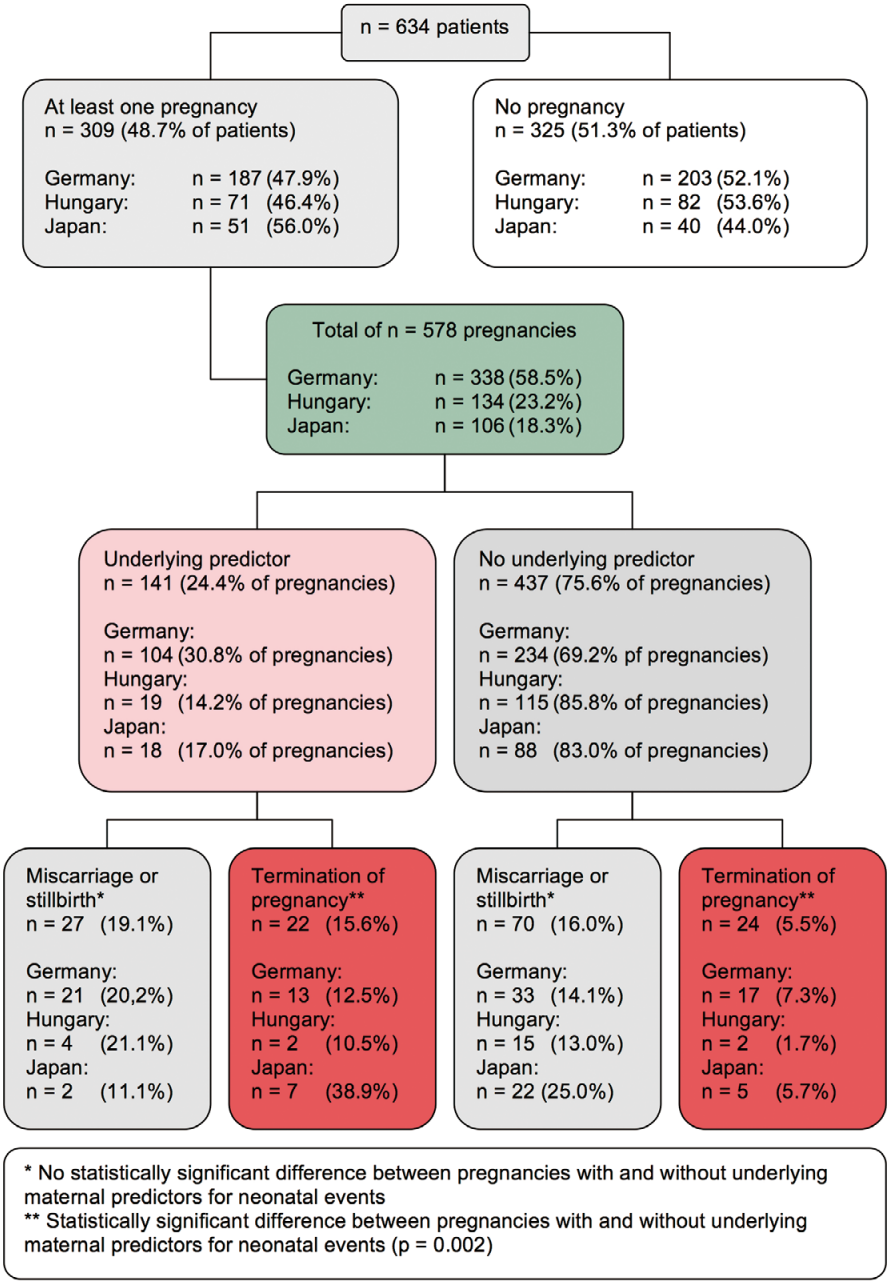

Figure. Course of the pregnancies of the women with congenital heart diseases in Germany, Hungary and Japan, in relation to the presence or absence of underlying predictors for neonatal complications.

Of these pregnancies, 24.8% (n=143) resulted in either miscarriage/stillbirth (16.8%, n=97) or TOP (8.0%, n=46).

At least 1 miscarriage was registered in 23.3% (n=72) of the patients and in 12.6% (n=39), TOP was performed; 9 women had at least 1 miscarriage/stillbirth, as well as at least 1 TOP. The most miscarriages/stillbirths and TOPs were recorded for the Japanese women, affecting 33.9% (n=36)/22.6% (n=24) and 11.3% (n=12), respectively. In Hungary, such an event occurred only approximately half as often (17.2%, n=23; of these miscarriages/stillbirths: 14.2%, n=19; TOP: 3.0%, n=4). Affecting n=84 (24.9%; of these miscarriages/stillbirths: 16.0%, n=54; TOP: 8.9%, n=30), the proportion of miscarriages/stillbirths and TOP among the German participants was somewhere in-between (**Figure**).

Courses of Pregnancy and Relationship to Maternal Predictors of Neonatal Complications

Among the study participants, 28.7% (n=182) had underlying maternal predictors for neonatal complications. In the German patients, such predictors were found most frequently (34.9%,

Table 3. Subjective Level of Information Concerning Pregnancy-Associated Risks Reported by Women With Congenital Heart Diseases

Reported level of information	Germany (n=390)	Hungary (n=153)	Japan (n=91)	Total (n=634)
Very good	125 (33.7)	24 (17.4)	22 (25.0)	171 (28.6)
Moderate	119 (32.1)	77 (55.8)	31 (35.2)	227 (38.0)
Very bad	127 (34.2)	37 (26.8)	35 (39.8)	199 (33.3)
Missing values	19	15	3	37

n=136), but less often in Japanese (22.0%, n=20) and Hungarian (17.0%, n=26) patients (Figure).

Of the 309 women who had been pregnant at least once, 24.3% (n=75) had underlying maternal predictors for neonatal complications. In these patients, a total of 141 pregnancies were observed.

Hence, 24.4% (141/578) of the pregnancies recorded were associated with at least 1 of the described predictors (Germany: n=104, 30.8%; Hungary: n=19, 14.2%; Japan: n=18, 17.0%).

A total of 34.8% (49/141) of all pregnancies with underlying maternal predictors for neonatal complications resulted in miscarriage or stillbirth or TOP.

In comparison, miscarriage, stillbirth or TOP occurred in 21.5% (94/437) of those pregnancies without underlying predictors (Figure).

With respect to the total study population, no significant difference was found between pregnancies with and without underlying maternal predictors for neonatal events as to the number of miscarriages and stillbirths.

However, a statistically significant difference (P=0.002) was found regarding the number of TOPs, but because of insufficient sample sizes, direct comparisons of the participating countries were not possible.

Patients' Subjective Level of Information Concerning Potential Pregnancy-Associated Cardiovascular Risks

Of the 634 patients surveyed, 33.3% indicated they were poorly informed about the potential risks of becoming pregnant.

The proportion was largest in Japan, where 39.8% (n=35) expressed this deficit; in Germany and Hungary, 34.2% (n=127) and 26.8% (n=37), respectively, stated they were poorly informed (Table 3).

Discussion

To our knowledge, the present study for the first time provides an overview of the frequency of miscarriages, stillbirths and TOP in a large collective of women with CHD, including a cultural and socioeconomic comparison of different countries.

In the majority of cases, pregnancy is well tolerated by women with CHD. However, the maternal risk of cardiovascular complications increases with increasing complexity of the underlying heart anomaly. In some patients with CHD, a pregnancy can even represent an unwarranted risk.[12–14] In addition, with 18% being affected, pregnant women with CHD carry also an increased risk of fetal and neonatal complications as compared with healthy women (7%).[15] In different studies, a connection between maternal cardiovascular and neonatal complications was observed.[6]

The present study revealed that in women with CHD, 25% of all pregnancies were terminated or resulted in miscarriage or stillbirth.

The frequency of miscarriages in healthy women is not known exactly; according to estimates, between 12% and 15% of all pregnancies are affected.[12,16] Regarding women with CHD, miscarriage was observed in 6–15% of all pregnancies.[6,7,12,15,17] Stillbirths occur much less frequently than miscarriages. The WHO in 2009 estimated the rate of stillbirths worldwide at 0.2–4.7% (average: 2%) of all pregnancies.[18,19] Concerning the rate of stillbirths in women with CHD, no current numbers are available.

Affecting 16.8% of all pregnancies recorded in the present survey (97/578), miscarriages and stillbirths were observed more frequently than described for the general population and, as yet, for patients with CHD.[7,12,15,16,19] However, it should be noted that precise numbers are elusive because of a high proportion of clinically unapparent miscarriages occurring during early pregnancy in both patient collectives. Nevertheless, the high rate of miscarriages should give reason to emphasize this issue and to timely inform patients about the risk of losing the child.

It is by all means possible that with the growing number of female patients with CHD desiring to get pregnant, the number of severe and very severe CHD might also increase, which, at the same time, might lead to an increasing frequency of neonatal complications in terms of miscarriage or stillbirth.

TOP, which is legal under similar conditions in all 3 participating countries, occurred in only 8% (46/578) of the observed pregnancies. This proportion is in the upper range given in the literature regarding the rate of TOP in women with CHD (5–8%).[7,12,20]

The overall rate of TOP in all 3 participating countries was lower than that in the European or Asian general public (30% and 22%, respectively). This might be attributed to a particularly strong desire of women with CHD to have a child and/or to the patient's fear that possible further pregnancies might be limited for them.

However, the possibility of socially desirable responses should be also considered regarding the present study. Thus, for instance, a questionnaire survey taking place against the background of public debate on the ethical issues regarding TOP can result in bias (ie, lower numbers of women stating they have had an induced abortion) despite being anonymous.[21,22]

The fact that, in all 3 participating countries, there was a considerable deficit regarding the level of the women's information on potential pregnancy-associated risks has major clinical importance. One-third of the study participants indicated they were poorly informed concerning such potential risks. The proportion of women feeling ill-informed was largest among the patients from Japan (40%), followed by Germany (34%) and Hungary (27%). This raises the fear that in many cases the chance to adequately inform patients at risk and to thus prevent them or their child from damage or hazard is being missed. In view of patient autonomy, adequate and

up-to-date patient education also poses an ethical challenge to those caring for women with CHD.[23]

In the presence of maternal predictors for neonatal events, miscarriage or stillbirth did not occur more frequently than in cases of no underlying predictors. In contrast, underlying maternal predictors did have an influence on the number of TOPs. These were observed 3-fold more in the group of pregnant women with underlying predictors for neonatal complications as compared with those without underlying predictors (15.6% vs. 5.5%).

As maternal cardiovascular complications during pregnancy, nor other neonatal complications, were not recorded in the present study, it is unknown if the higher number of TOPs is to be attributed to the presence of medical indications for maternal complications.

Moreover, it might also be the case that women with CHD were confronted with potential risks only after becoming pregnant, leading to them to choose an abortion. The reasons why women with CHD with underlying maternal predictors for neonatal complications opted for TOP more frequently has to be investigated in further studies.

Furthermore, investigating the clinical relevance of single predictors seems to be important in order to derive operating guidelines for clinical practice.

In any case, it is to be recommended that pregnant patients with CHD should be attended to and counseled individually by cardiologists, gynecologists, obstetricians and anesthetists with relevant expert knowledge.[24–27] This applies to severe CHD in particular, but also to mild defects if the treating physicians lack experience with this particular problem.

Study Limitations

The conclusions of the present study are limited by the fact that it was a quantitative cross-sectional study conducted at specialized centers. The study participants thus do not necessarily reflect the patient collective usually encountered by cardiologists or gynecologists in private practice or at centers not specializing in ACHD. However, because of the sample size, it can be assumed that the presented results sufficiently reflect the cohort of women with CHD.

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References

1. Moons P, Bovijn L, Budts W, Belmans A, Gewillig M. Temporal trends in survival to adulthood among patients born with congenital heart disease from 1970 to 1992 in Belgium. *Circulation* 2010; **122:** 2264–2272.
2. Kaemmerer H, Schneider KTM, Niesert S, Hess J. Schwangerschaft bei Frauen mit angeborenen Herzfehlern. *Gynäkologe* 1999; **32:** 377–385.
3. Uebing A, Gatzoulis MA, von Kaisenberg C, Kramer HH, Strauss A. Congenital heart disease in pregnancy. *Dtsch Arztebl Int* 2008; **105:** 347–354.
4. JCS Joint Working Group. Guidelines for indication and management of pregnancy and delivery in women with heart disease (JCS 2010): Digest version. *Circ J* 2012; **76:** 240–260.
5. European Society of Gynecology (ESG); Association for European Paediatric Cardiology (AEPC); German Society for Gender Medicine (DGesGM), Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J* 2011; **32:** 3147–3197.
6. Drenthen W, Boersma E, Balci A, Moons P, Roos-Hesselink JW, Mulder BJ, et al. Predictors of pregnancy complications in women with congenital heart disease. *Eur Heart J* 2010; **31:** 2124–2132.
7. Khairy P, Ouyang DW, Fernandes SM, Lee-Parritz A, Economy KE, Landzberg MJ. Pregnancy outcomes in women with congenital heart disease. *Circulation* 2006; **113:** 517–524.
8. Lu CW, Shih JC, Chen SY, Chiu HH, Wang JK, Chen CA, et al. Comparison of 3 risk estimation methods for predicting cardiac outcomes in pregnant women with congenital heart disease. *Circ J* 2015; **79:** 1609–1617.
9. Rasch B, Friese M, Hofmann WH, Naumann E. Quantitative Methoden, Band 1, 2nd edn. Berlin: Springer, 2006; 57.
10. Perloff JK, Child JS, Aboulhson J. Congenital heart disease in adults, 3rd edn. Philadelphia: WB Saunders, 2008.
11. Warnes CA, Liberthson R, Danielson GK, Dore A, Harris L, Hoffman JL, et al. Task force 1: The changing profile of congenital heart disease in adult life. *J Am Coll Cardiol* 2001; **37:** 1170–1175.
12. Drenthen W, Pieper PG, Roos-Hesselink JW, van Lottum WA, Voors AA, Mulder BJ, et al. Outcome of pregnancy in women with congenital heart disease: A literature review. *J Am Coll Cardiol* 2007; **49:** 2303–2311.
13. Thorne S, MacGregor A, Nelson-Piercy C. Risks of contraception and pregnancy in heart disease. *Heart* 2006; **92:** 1520–1525.
14. Trigas V, Nagdyman N, Pildner von Steinburg S, Oechslin E, Vogt M, Berger F, et al. Pregnancy-related obstetric and cardiologic problems in women after atrial switch operation for transposition of the great arteries. *Circ J* 2014; **78:** 443–449.
15. Siu SC, Colman JM, Sorensen S, Smallhorn JF, Farine D, Amankwah KS, et al. Adverse neonatal and cardiac outcomes are more common in pregnant women with cardiac disease. *Circulation* 2002; **105:** 2179–2184.
16. García-Enguídanos A, Calle ME, Valero J, Luna S, Domínguez-Rojas V. Risk factors in miscarriage: A review. *Eur J Obstet Gynecol Reprod Biol* 2002; **102:** 111–119.
17. Siu SC, Sermer M, Colman JM, Alvarez AN, Mercier LA, Morton BC, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001; **104:** 515–521.
18. Cousens S, Blencowe H, Stanton C, Chou D, Ahmed S, Steinhardt L, et al. National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: A systematic analysis. *Lancet* 2011; **377:** 1319–1330.
19. Stauber M, Weyerstahl T. Duale Reihe Gynäkologie und Geburtshilfe, 2nd edn. Stuttgart: Georg Thieme Verlag, 2005.
20. Sedgh G, Singh S, Shah IH, Ahman E, Henshaw SK, Bankole A. Induced abortion: Incidence and trends worldwide from 1995 to 2008. *Lancet* 2012; **379:** 625–632.
21. Bortz J, Döring N. Forschungsmethoden und Evaluation. Berlin: Springer, 1995; 212–213.
22. Amelang M, Bartussek D, Stemmler G, Hagemann D. Differentielle Psychologie und Persönlichkeitsforschung, 6th edn. Stuttgart: Kohlhammer, 2006.
23. Geisler LS. Patient autonomy: A critical concept analysis. *Dtsch Med Wochenschr* 2004; **129:** 453–456.
24. Kaemmerer M, Vigl M, Seifert-Klauss V, Nagdyman N, Bauer U, Schneider KT, et al. Counseling reproductive health issues in women with congenital heart disease. *Clin Res Cardiol* 2012; **101:** 901–907.
25. Vigl M, Kaemmerer M, Niggemeyer E, Nagdyman N, Seifert-Klauss V, Trigas V, et al. Sexuality and reproductive health in women with congenital heart disease. *Am J Cardiol* 2010; **105:** 538–541.
26. Vigl M, Kaemmerer M, Seifert-Klauss V, Niggemeyer E, Nagdyman N, Trigas V, et al. Contraception in women with congenital heart disease. *Am J Cardiol* 2010; **106:** 1317–1321.
27. Warnes CA. Pregnancy and delivery in women with congenital heart disease. *Circ J* 2015; **79:** 1416–1421.