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Menstrual Cycle and its Disorders in Women with Congenital Heart Disease

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ABSTRACT

Objectives. To investigate the age at menarche, the prevalence of menstrual cycle (interval) disorders, and determinants in women with congenital heart disease (CHD).

Design. Using two CHD registries, 1802 (82%) of the 2196 women with CHD contacted (aged 18–58 years) provided written informed consent. After exclusion of patients with genetic disorders known to be associated with menstrual cycle disorders, 1593 eligible patients remained. Interviews by telephone and reviews of medical records were conducted.

Results. Overall, the age at menarche was slightly increased in women with CHD (13.3 vs. 13.1 years in the general population), mainly attributable to an increased prevalence of primary amenorrhea (n = 147; 9.2%). Other menstrual cycle disorders were documented: secondary amenorrhea (n = 181, 11.4%), polymenorrhea (n = 103, 6.5%), oligomenorrhea (n = 90, 5.6%), and menorrhagia (n = 117, 6.5%). The occurrence of these disorders also depended on the presence of cyanotic heart disease, surgical status, the number of surgical interventions, and the severity of CHD.

Discussion. Menstrual cycle disturbances, in particular primary amenorrhea, were frequently observed in this population. Patients with complex (cyanotic) heart disease needing repeated surgical interventions prior to menarche are especially at risk.

Key Words. Congenital Heart Disease; Menstrual Cycle; Amenorrhea

Introduction

Menstrual function is an important aspect of normal female physical and psychological development. Disturbances of this menstrual cycle have a significant impact on a patient's quality of life and may be associated with (sub)-infertility.

In women with complex congenital heart disease (CHD), menstrual cycle disorders have been described. Both Canobbio and Drenthen et al. showed that in women with a Fontan procedure, the age of menarche was delayed. The average age at menarche in these studies was higher due to an increased prevalence of primary amenorrhea.[1,2]

It has been hypothesized that exposure to chronic hypoxemia in the context of cyanotic CHD influences ovarian function with subsequent menstrual cycle abnormalities. It may be speculated that surgical interventions early in life may influence ovarian function. Furthermore, it can be hypothesized that chronic systemic venous congestion, pulmonary hypertension, concomitant cardiac medication, residual valvular heart disease, and the recurrence of rhythm disorders with their hemodynamic consequences could impact gynecological health.

The primary objective of the present study is to give a cross-sectional description of the menstrual

cycle and its disorders in a large cohort of women with CHD. A secondary objective was to compare the results with the number of incidence and prevalence found in the general population, and to identify possible CHD-related predictors of these menstrual cycle disorders.

Patients and Method

For the present study, 2196 female patients with CHD aged 18–58 years were drawn from the nationwide CONgenital CORvitia (CONCOR) registry and a Belgian tertiary medical center's adult CHD database. Together, these registries had included 8035 patients with CHD at study selection. Overall, 1802 patients consented to participate. Females with identified genetic disorders (see below) were eliminated from the study. The institutional review board or ethics committee of the seven participating tertiary centers approved the study protocol.

Basic native anatomy, prior surgical procedures, comorbidities, and medical history were recorded using the European Pediatric Cardiac Coding system. Patients were asked by telephone to complete a questionnaire, which included questions concerning their age at menarche and visits to the gynecologist due to menstrual cycle disorders. In case a patient had visited the gynecologist for menstrual cycle disorders, their medical files were reviewed. Detailed information (cycle duration, regularity) was retrieved regarding the patient's most recent menstrual cycle not influenced by the use of contraception or other types of hormone therapy. This cycle needed to be at least three months after cessation of this therapeutic intervention, but not within the first year after menarche.

Study endpoints (according to the Dutch and Belgian gynecology societies at the time of study design) included: (1) primary amenorrhea (menarche not established by the 16th birthday; (2) secondary amenorrhea (absence of menstruation for 180 days or more after the patient had had her menarche); (3) oligomenorrhea or infrequent bleeding (menstrual bleeding at intervals >35 days); (4) polymenorrhea or frequent bleeding (menstrual bleeding at intervals <24 days); (5) menorrhagia (excessive or prolonged [>7 days] menstrual bleeding occurring at regular intervals characterized by loss of blood clots or development of anemia).

Using a Clinitrial data-entry program (Clinitrial, Phase Forward, Waltham, MA) to record information, the data was converted to SPSS (version 11.0; SPSS Inc., Chicago, IL) for statistical analysis. Descriptive statistics for nominal data were expressed in absolute numbers and percentages. Mean values and standard deviations were calculated for normally distributed continuous variables after checking for normality. Medians and quartiles were computed for continuous variables with non-normal distribution. Univariable binary logistic regression was performed to identify possible CHD-related predictors of menstrual cycle disorders, such as any surgical palliation or correction prior to menarche (number of interventions, divided into the following four categories: uncorrected, corrected, palliated + corrected, and corrected), age at correction, the presence of cyanosis, "in origin/at birth" cyanotic heart disease, and disease severity according to the American College of Cardiology (ACC) Task Force 1, the known underlying gynecological disease and the above-mentioned endpoints.[3] Data of these regression analyses are presented as odds ratio (OR) ± 95% confidence intervals (CI) and their subsequent *P* values. Multivariable age-corrected models were constructed per endpoint using the univariable predictors with a cut-off *P* value of <.10. All tests performed to test the zero hypotheses were two-sided. A *P* value <.05 was considered statistically significant.

Results

Baseline characteristics of the enrolled 1802 patients (participation rate 82%) are summarized in Table 1. Genetic disorders were diagnosed in 209 patients, including Marfan (n = 131), Down (n = 33), Turner (n = 19), Noonan (n = 9), and other syndromes (n = 17, mainly based on associated malformations or malfunction of the uterus or ovaries); these patients were eliminated from the final analysis.

An overview of the mean age at menarche, average cycle length, and menstrual cycle disorders per CHD category for the remaining 1593 subjects is depicted in Table 2. The mean age at menarche was 13.3 ± 1.5 years, which is slightly higher than the 13.15 years found in the general population in the Netherlands. In addition, it was found that irrespective of surgical status, menarche was delayed in females with "in origin" cyanotic heart disease (13.5 years).

Figure 1 illustrates the effects of surgical status, the number of surgical interventions prior to menarche and CHD severity upon the age that

Table 1. Baseline Characteristics of the 1802 Enrolled Women with Congenital Heart Disease Prior to Menarche*

	n = 1802
Mean age at inclusion (years)	**31.6 ± 8.1**
CHD diagnosis	
Septal defects	536 (29.7)
Right ventricular outflow tract obstruction	214 (11.9)
Tetralogy of Fallot	204 (11.3)
Aortic coarctation	181 (10.0)
Left ventricular outflow tract obstruction	157 (8.7)
Complete transposition of great arteries	91 (5.0)
Pulmonary hypertension (including Eisenmenger)	26 (1.4)
Complex CHD	128 (7.1)
Other CHDs	134 (7.4)
Marfan	131 (7.3)
Palliative surgery prior to menarche	215 (11.9)
Median age at palliation (years)	1 (range 0–16)
Type of initial palliative surgery	
Blalock–Taussig	43
Waterston shunt	36
Rashkind atrio-septostomy	41
Blalock–Hanlon	16
Pulmonary artery banding	29
Fontan circulation	14
Other	36
Corrective surgery prior to menarche	827 (45.9)
Mean age at correction (years)	5.1 ± 3.4
Number of surgical interventions prior to menarche	
none	894 (49.6)
1	666 (37.0)
2	173 (9.6)
More than 2	69 (3.8)
Medical history prior to menarche:	
Arrhythmias	5 (0.3)
Heart failure	0
Cerebrovascular accident	7 (0.4)
Endocarditis	6 (0.3)

*Number of patients (%) unless otherwise documented.

patients reach menarche. No correlation between the age at correction and age at menarche was found.

One hundred forty-seven (9.2%) women with CHD met the criteria of primary amenorrhea. Univariable binary logistic regression showed that patients who were only palliated prior to menarche ($P < .001$), patients with a higher number of surgical interventions ($P = .001$), those with "in origin" cyanotic heart disease ($P = .01$), and those with severe CHD (in comparison with simple defects: $P < .001$) were at higher risk. Multivariable binary logistic regression corrected for the patients' age and, when applicable, gynecological abnormalities showed that only having had palliative surgery (OR 2.43, 95% CI 1.30–4.54; $P = .006$) and severity of CHD (OR 2.08, 95%CI 1.25–3.47; $P = .005$) remained independent predictors of primary amenorrhea.

In total, 181 (11.4%) women with CHD reported at least one episode of secondary

Table 2. Mean Age at Menarche, Average Cycle Length and Menstrual Cycle Disorders per Congenital Heart Disease in 1593 Women with Congenital Heart Disease (Excluding 209 Patients with Genetic Disorders)*

CHD diagnosis	Number of patients	Mean age at menarche (years)	Mean cycle length (days)	Cycle length (10th + 90th percentile)	Primary amenorrhea (%)	Secondary amenorrhea (%)	Menorraghia (%)	Oligomenorrhea (%)	Polymenorrhea (%)	≥1 Menstrual cycle disorder (%)
Septal defects	505	13.3	28.4	25–30	47 (9.3)	2 (12.3)	56 (11.1)	32 (6.3)	46 (9.1)	189 (37.4)
RVOT obstruction	201	13.4	28.8	27–31	17 (8.5)	23 (11.4)	6 (3.0)	12 (5.0)	10 (5.0)	57 (28.4)
Tetralogy of Fallot	195	13.1	28.3	27–29	9 (4.6)	15 (7.7)	9 (4.6)	9 (4.6)	9 (4.6)	47 (24.1)
Aortic coarctation	170	13.3	28.2	27–30	10 (5.9)	13 (7.6)	4 (4.1)	5 (2.9)	8 (4.7)	32 (18.8)
LVOT obstruction	153	13.0	28.3	25–30	7 (4.6)	21 (13.7)	6 (3.9)	6 (3.9)	12 (7.8)	48 (31.4)
TGA	91	13.7	28.2	27–29	15 (16.5)	11 (12.1)	1 (1.1)	4 (4.4)	1 (1.1)	30 (33.0)
PHT	24	13.8	28.7	27–31	3 (12.5)	6 (25.0)	2 (8.3)	1 (4.2)	2 (8.3)	12 (50.0)
Complex CHD	123	14.1	28.7	26–33	28 (21.9)	20 (15.6)	15 (11.7)	10 (7.8)	7 (5.5)	62 (50.4)
Other CHD	131	13.3	29.5	25–33	11 (8.4)	10 (7.6)	15 (11.5)	11 (8.4)	8 (6.1)	41 (31.3)
Total	1593	13.3	28.5	26–30	147 (9.2)	81 (11.4)	17 (7.3)	90 (5.6)	103 (6.5)	518 (32.5)

*Number of patients (%) unless otherwise documented.
CHD, congenital heart disease, LVOT, left ventricular outflow tract, PHT, pulmonary hypertension (including Eisenmenger), RVOT, right ventricular outflow tract, TGA, complete transposition of the great arteries.

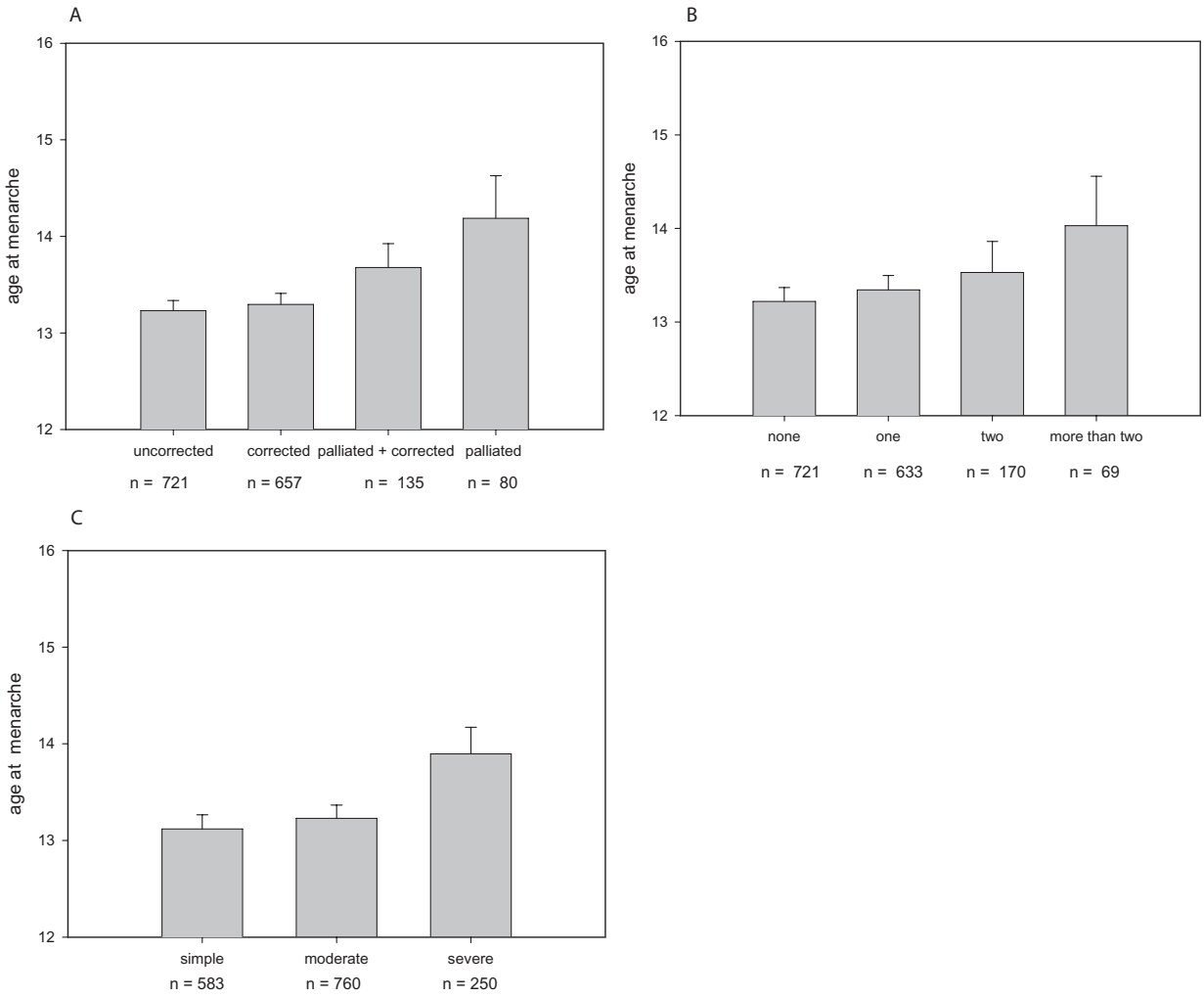

Figure 1. (A) Effect of surgical status prior to menarche on the age menarche is reached (B) Effect of the number of surgical interventions prior to menarche on the age menarche is reached. (C) Effect of disease severity according to the ACC Task Force[3] on the age menarche is reached.

amenorrhea, 31 of whom underwent evaluation by a gynecologist. Diagnoses for secondary amenorrhea included ovarian disease (n = 13), (premature) ovarian failure (n = 6), endometriosis (n = 4), polycystic ovarian syndrome (n = 3), functional hypothalamic dysfunction (n = 10), and endocrinological disease (n = 4; 2 secondary to thyroid disease, and 2 pituitary disease). Four patients were found to have anatomical uterine disease, including one Asherman's syndrome. For the remaining 150 patients, no medical evaluation was given for the reported secondary amenorrhea. Patients self-reported what they felt may have caused the episode of secondary amenorrhea. These included health problem and/or deterioration of their CHD (n = 17), surgery for heart disease (n = 16), extreme weight loss or anorexia (n = 15), emotional stress (n = 12), post-pregnancy recovery (n = 12), and having been involved in strenuous exercise/sport (n = 5) at the time of secondary amenorrhea. The remaining patients could not explain the episode(s) of secondary amenorrhea. The persistence of cyanosis beyond menarche predicted the occurrence of secondary amenorrhea (OR 3.17, 95% CI 1.52–6.58; $P = .002$).

Oligomenorrhea was reported by 5.6% (n = 90) of the women with CHD. When corrected for age and known underlying gynecological disease, a trend towards more frequent occurrence of oligomenorrhea in patients with a higher number of surgical interventions ($P = .064$) became apparent. In the sample, 6.5% (n = 103) reported average cycle lengths of <24 days. Again, no univariable predictors could be identified.

Menorrhagia was reported in 117 (7.3%) women. Women who were corrected ($P < .001$) or a higher number of surgical interventions ($P = .040$) appeared be at lower risk of developing menorrhagia. Multivariable analysis showed that, when corrected for age, only an uncorrected surgical status was an independent predictor of menorrhagia (OR 1.90, 95% CI 1.27–2.86; $P = .002$). In 30 women, the cause of the menorrhagia was known: structural (intra-uterine) lesions (n = 11, 37%, mainly myomas), anticoagulation (n = 3, 10%), and other gynecological disorders (n = 16, 53%). In most patients, the cause was unknown.

Discussion

The present study shows that age at menarche is slightly delayed in women with CHD, mainly attributable to the high rate of primary amenorrhea. Patients that only underwent palliative surgery and those with more severe CHD appear to be at higher risk of primary amenorrhea. Moreover, the occurrence of secondary amenorrhea and oligomenorrhea also appear excessive.

The age at menarche appears to be delayed in women with CHD. Canobbio et al. reported a similar (also significantly delayed) age at menarche (13.4 years) in their cohort of 98 women with CHD.[4] In women with cyanotic CHD, they found that menarche occurred even later (13.9 years). In the present study, menarche appears to be particularly delayed in those patients with "in origin" cyanotic CHD and those with complex CHD. Patients that remained cyanotic prior to menarche reached menarche at an age comparable with patients with "in origin" cyanotic CHD. As the objective of corrective surgery is to resolve cyanosis, the age at repair can be considered a surrogate variable indicating the duration of hypoxia exposure. The age at correction, however, was not correlated with the patients' age at menarche. This implies that the duration of exposure to relative hypoxemia does not appear to gravely affect the age at menarche in patients with CHD. The effect of cyanosis severity could not be investigated in the present study due to missing data. In addition to cyanosis, hemodynamic factors may play an important role. Since the early seventies, ovarian blood flow has been suggested as an important determinant of ovarian function.[5,6] We hypothesize that forward failure of the systemic ventricle and venous congestion may interfere with the oxygen and nutritional support essential for normal ovarian function. Prospective research is needed to investigate if and how ovarian blood flow is influenced by the presence of, in particularly, complex CHD.

It appears that for every surgical procedure performed prior to menarche, menarche is postponed for a certain amount of time. The time span between surgical intervention and menarche, however, did not affect the age at menarche. Several explanations could be proposed. Each intervention performed may damage ovarian function due to the hemodynamic shifts during the procedures, the administration of (anesthetic and analgesic) drugs, or as simple as activation of the sympathetic nervous system based on "fright and flight" survival mechanism. The ovaries need time to recuperate after the event. Then again, the CHD patients who need several surgical interventions as well as the "in origin" cyanotic CHD patients are patients with generally more severe diseases. Also, the surgical status prior to menarche depicted in Figure 1 strengthens this assumption. It is, therefore, plausible that age at menarche merely reflects the severity of the underlying CHD. By this mechanism, procreation is guaranteed for those patients physically suitable for this important feature of human nature.

Primary amenorrhea generally occurs in 0.1–2.5% of women in the general population. In patients with CHD, this was remarkably higher. In concordance with the factors associated with a higher age at menarche, significant predictors of primary amenorrhea were, a higher number of surgical interventions prior to menarche, "in origin" cyanotic heart disease, and having only had palliative surgery. These factors, therefore, do not appear to interfere with normal growth and secondary sexual development. Diagnostic tests to pinpoint the cause of primary amenorrhea were not performed in all patients. As a consequence, certain causes cannot be ruled out with confidence. Conversely, the fact that most patients reached menarche without surgical or other sort of gynecological intervention suggests a more functional deficiency, rather than anatomical or genetic disorders.

Cannobio was also the first to report other menstrual cycle disturbances among patients with CHD. In their cohort of patients who had undergone Fontan palliation, a subset of patients reported dysfunctional bleeding evidenced by complaints of oligomenorrhea, menorrhagia, and amenorrhea.[1] It was suggested that there could

be a relation with the duration of cyanosis after menarche, although the exact cause remained to be elucidated. In a subsequently conducted study in a tertiary cohort of CHD patients, Canobbio et al. indicated that menstrual patterns were similar to those of the general population. In patients who remained cyanotic, however, delay of menarche and an increased incidence of cycle lengths of shorter (<25 days) and longer (>35 days) duration were observed.[4]

The occurrence of ≥1 episode of secondary amenorrhea is also remarkably high (10.3%), while only 0.7–3.0% of the women in the general population report this menstrual cycle disturbance. In the patients that sought gynecological care, the distribution of diagnoses that explained the secondary amenorrhea did not differ from that found in the general population: ovarian disease (42 vs. 40%), hypothalamic dysfunction (32 vs. 35%), endocrine disorders (13 vs. 19%), and uterine disease (13% vs. 5%). Patients who were cyanotic prior to menarche appear to be at greater risk of developing secondary amenorrhea. Oligomenorrhea also appears to be common in women with CHD, though comparative data of the general population are lacking. Again, the number of surgical interventions prior to menarche surfaces as a potential predictor. Importantly, patients with primary amenorrhea were not the same patients as those that developed secondary amenorrhea or oligomenorrhea. A similar etiology of the three thus far discussed complaints remains possible. Functional hypothalamic amenorrhea is a common cause of both amenorrhea and oligomenorrhea. It is a disorder that, by definition, excludes pathologic disease, and is characterized by a decrease in hypothalamic gonadotropin-releasing hormone secretion. Multiple factors may contribute to the pathogenesis of functional hypothalamic amenorrhea, including eating disorders, such as anorexia nervosa, exercise, and stress. The self-reported causes of secondary amenorrhea in women with CHD included several factors that may have contributed (see Results section, page 4).

Menorrhagia was mainly reported by patients with uncorrected CHD. The concomitant use of anticoagulation appears to increase the risk of menorrhagia, though no significant relationship was found. In the general population, the main causes are systemic illness (e.g., hypothyroidism) and intra-uterine lesions (e.g., myomas). Coagulopathies secondary to hematological disorders (for example, von Willebrands disease) or malignancy are relatively rare. In our patients, the presence of CHD may be the systemic illness responsible for most cases of menorrhagia; nevertheless, this needs to be investigated in a prospective fashion.

Several potential limitations must be noted. The retrospective design necessitated a review of patient's medical records, and consequently, missing values are inevitable. The exclusion of patients with genetic disorders introduced a selection bias as would the inclusion of these disorders. The definitions of the used endpoints are currently subject of debate and are, therefore, not universally agreed upon. Recall bias may have influenced the results obtained by questionnaires. The present study should be seen as a descriptive, and therefore, hypothesis-generating study. We were insufficiently informed on the body mass index of our patients at the time of menarche. Since weight is an important factor, and cachexia is known to delay menarche, this may have influenced the outcome of the present study. Conclusions on causality of the observed relations cannot be drawn with confidence due to the lack of clinical gynecological evaluation and laboratory measurements of hormone levels. A prospective case-control design would be useful and could improve the level of statistical proof.

In conclusion, this hypothesis-generating study suggests that menarche appears to be slightly delayed in women with CHD. A high prevalence of primary amenorrhea was especially observed. Moreover, several disorders of the menstrual cycle appear more prevalent. The type of CHD (cyanotic vs. acyanotic), the persistence of cyanosis, and the number of surgical interventions prior to menarche appear to predict the occurrence of these disorders. The results are suggestive of a "functional" common pathway that needs further exploration.

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