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Original Article

Oral contraceptive use and conotruncal congenital heart disease

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Abstract

Background Congenital heart disease (CHD) represents some of the more prevalent malformations among live births and remains the leading cause of death from congenital malformations. Conotruncal anomalies comprise a diverse group of CHD involving the outflow tracts of the heart and the great vessels. Oral contraceptive exposure before pregnancy may be one of the risk factors for conotruncal CHD.

Objective To evaluate the effect of oral contraceptive use before pregnancy on the risk of conotruncal CHD in children.

Methods A case-control study was conducted from July 2010 until July 2011 in Haji Adam Malik Hospital, Medan. Subjects with CHD were divided into two groups: conotruncal CHD as the case group and non-conotruncal CHD as the control group. Both groups had mothers with and without histories of oral contraceptive use before pregnancy. Parents were interviewed using questionnaires. Statistical analyses were performed using Chi-square test, student's T-test, and Mann Whitney test.

Results A total of 80 subjects were eligible, with 40 subjects in each group. The percentages of subjects whose mothers used oral contraceptives were 62% of the conotruncal CHD group and 60% of the non-conotruncal CHD group (OR 0.82; 95%CI 0.33 to 1.98). The mean duration of maternal oral contraceptive use before pregnancy was 19.1 months for the case group and 18.8 months for the control group (P=0.87).

Conclusion In children with CHD, maternal oral contraceptive use before pregnancy does not appear to increase the risk of conotruncal CHD. **[Paediatr Indones. 2014;54:309-13.]**

Keywords *oral contraceptive exposure, conotruncal congenital heart disease*

The World Population Data Sheet in 2000 ranked Indonesia as the fifth largest in terms of population. The aim of the *National Family Planning Program* (KB) in Indonesia was to realized "Qualified Family in 2015". The program aimed to promote contraceptive use for married couples, as well as to reduce the number of pregnancies and the growth rate of the general population.[1]

Hormonal contraception is one of the most effective and most used contraceptive methods. Oral contraception in the pill form is effective because it is reliable, reversible, can be used by all women of reproductive age as an emergency contraceptive, is easily terminated at any time, with fertility returning immediately following termination. Oral contraceptives comprise either estrogens or progestins, or a combination of the two hormones.[2]

Congenital heart disease is a category of cardiac defects characterized by gross structural abnormalities of the heart or great vessels that

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actually or potentially interfere with normal cardiac function. In the spectrum of all congenital disorders, heart malformations account for one-third of major birth defects. The cause of cardiac abnormalities is largely unknown. Embryogenic exposure during the cardiogenesis period to substances, such as alcohol, anti-convulsants, sedatives, or oral contraceptives may increase the risk of CHD.[3] Conotruncal CHDs are also known as outflow tract defects. Tetralogy of Fallot (ToF), double outlet right ventricle (DORV), transposition of the great arteries (TGA), and persistent truncus arteriosus (PTA), are common types of conotruncal CHDs.[4] In the context of CHD, the embryo is most vulnerable to cardiopathic events at the time between germ layer differentiation and completion of cardiogenesis. This period corresponds to days 20 through 45 of human embryo development. Nonetheless, the timing of exposure may not always correlate with developmental deviation.[4,5]

Oral contraceptives have been suspected teratogens, especially those containing progesterone. The teratogenic effect of progesterone is unclear because research has been limited to animal studies.[5] The aim of this study was to evaluate the effect of oral contraceptive use before pregnancy on the risk of conotruncal CHD in children.

Methods

A case-control study was conducted from July 2010 until July 2011 in children who were clinic outpatients, or hospitalized in the Pediatric and Neonatology Ward of H. Adam Malik Hospital, North Sumatera. Subjects were collected by consecutive sampling and included infants and children up to age 18 years who were diagnosed with conotruncal or non-conotruncal CHDs by echocardiography. Subjects' mothers were with or without histories of oral contraceptive use before pregnancy.

Data were obtained from medical records. Parents were interviewed by filling questionnaires. All patients recorded their identity, i.e., name, date of birth, age, sex, address, parents' name, and contact phone number. The case group included children diagnosed with conotruncal CHD. The control group included children with non-conotruncal CHD.

This study was approved by the Ethics Committee of the University of North Sumatra Medical School. Data was analyzed using *SPSS version 17.0*. The significance level was accepted as $P<0.05$ and 95% confidence interval (CI). Chi square test was used to evaluate for an association between maternal oral contraceptive use before pregnancy and conotruncal CHD. Student's T-test was used to assess the duration of oral contraceptive use in conotruncal CHD. Mann Whitney test was used to assess the duration of discontinuation of oral contraceptive use for conotruncal CHD.

Results

During the study period, 80 children were diagnosed with CHD. Among the 40 children with conotruncal CHD, 22 children had mothers with a history of oral contraceptive use before pregnancy. In the control group, of the 40 children with non-conotruncal CHD, 24 children had mothers with a history of oral contraceptive use before pregnancy (**Figure 1**).

The median ages of children were 24.0 months and 12.5 months, in the case and control groups,

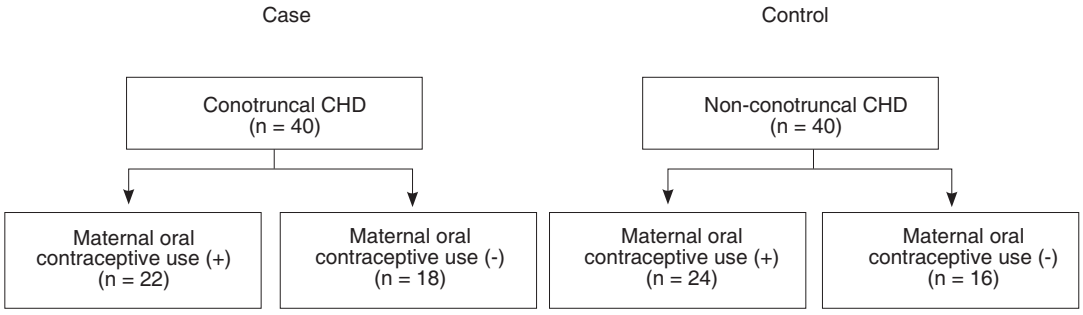

Figure 1. Study profile

respectively. In the case group, 26 children (65%) were male. In the control group, 29 children (72.5%) were female. The mean weight and height in the case group were higher than in the control group. The most common types of CHD were ToF (72.5%) in the case group and VSD (50.0%) in the control group (**Table 1**).

Table 2 shows that 62% of children in the case group and 60% of children in the control group had mothers who used oral contraceptives (OR 0.82; 95%CI 0.33 to 1.98). We found no significant association between oral contraceptive use before pregnancy and conotruncal CHD.

Table 3 shows that duration of discontinuation of oral contraceptive use prior to pregnancy in the conotruncal type CHD case group was not significantly different from that of the control group (P = 0.335).

Table 4 shows that there was no significant difference in duration of oral contraceptive use before pregnancy with conotruncal CHD between the two groups (P = 0.87).

Discussion

The incidence of conotruncal CHD differs between

Table 1. Characteristics of subjects

Characteristics	Case (n=40)	Control (n=40)
Median age (range), months	24.0 (0.1-168.0)	12.5 (0.2-168.0)
Gender, n (%)		.
Male	26 (65.0)	11 (27.5)
Female	14 (35.0)	29 (72.5)
Median weight (range), kg	10.5 (2.4-36.0)	7.8 (2.4-35.0)
Median height (range), cm	70.5 (48.5-120.5)	60.5 (48.5-125.0)
Median maternal age (range), years	27.0 (20.0-33.0)	26.0 (20.0-34.0)
Diagnosis, n (%)		
Tetralogy of Fallot	29 (72.5)	
Transposition of the great arteries	10 (25.0)	
Double outlet right ventricle	1 (2.5)	
Ventricular septal defect		20 (50.0)
Patent ductus arteriosus		12 (30.0)
Atrial septal defect		8 (20.0)
Paternal ethnicity, n (%)		
Javanese	22 (55.0)	26 (65.0)
Batak	11 (27.5)	12 (30.0)
Acehnese	3 (7.5)	1 (2.5)
Malay	2 (5.0)	1 (2.5)
Chinese	2 (5.0)	-
Maternal ethnicity, n (%)		
Javanese	13 (32.5)	15 (37.5)
Batak	13 (32.5)	13 (32.5)
Malay	9 (22.5)	9 (22.5)
Acehnese	3 (7.5)	2 (5.0)
Minang	2 (5.0)	1 (2.5)
Monthly family income, n (%)		
IDR < 1 million	-	2 (5.0)
IDR 1-1.5 million	10 (25.0)	11 (27.5)
IDR 1.5-2 million	13 (32.5)	16 (40.0)
IDR > 2 million	17 (42.5)	11 (27.5)

Table 2. Oral contraceptive use and conotruncal CHD

Oral contraceptive use	Case n (%)	Control n (%)	OR	95%CI
Yes	22 (62)	24 (60)	0.815	0.335 to 1.980
No	18 (45)	16 (40)		

Table 3. Duration of discontinuation of maternal oral contraceptive use

	Median duration of discontinuation of oral contraceptives prior to pregnancy		P value
	n	Months (range)	
Conotruncal case group	22	3.0 (1.0 – 9.0)	0.335
Non-conotruncal control group	24	2.0 (1.0 – 8.0)	

Table 4. Duration of oral contraceptive use

	Mean duration of oral contraceptive use		P value
	n	Months (SD)	
Conotruncal case group	22	19.1 (6.19)	0.87
Non-conotruncal control group	24	18.8 (4.11)	

genders. Tetralogy of Fallot, DORV, and TGA are more common among males than females, while persistent truncus arteriosus is more common among females, although several studies showed no statistically significant difference between genders.[7] In our study, 19 children with ToF were male (65.5%), 6 children with TGA (60%) were male, and only 1 male had DORV.

The cause of cardiac abnormalities is largely unknown. Genetic factors have been associated with CHD. A descriptive study of cardiac defects based on data from three large population-based registries in California, Sweden, and France, found that several conotruncal CHDs are associated with chromosomal abnormalities such as trisomy 21, trisomy 13, and trisomy 18.[8] A Philadelphia study found that chromosome 22q11 deletions are present in the majority of patients with DiGeorge syndrome, velocardiofacial, and conotruncal anomalies. Patients were evaluated for chromosomal deletions by *fluorescence in situ hybridization* (FISH). These results began attempts to define guidelines for deletion screening of patients with conotruncal CHD.[9]

An Atlanta study showed that maternal age of 35 to 40 years increased the risk of all heart defects (OR 1.12; 95%CI 1.03 to 1.22).[10] In our study, the maternal age range among case and control subjects was 20 to 34 years, with 19 mothers aged ≥ 30 years (23.75%). A California case-control study had 277 patients with conotruncal CHD. The authors found that socioeconomic status was not associated with increased risk of conotruncal CHD.[11] In our study, subjects were from middle income families. We did not perform a statistical analysis to determine the relationship between socioeconomic status or maternal education level to conotruncal CHD. A relationship between conotruncal CHD and race or ethnicity remains unclear. A Florida study found higher rates among in whites and Hispanics than in African-Americans for TGA, ToF, and PTA.[12] Our subjects ethnicities were Javanese, Malay, Batak, Acehnese, and Minang. In some cases, the paternal and maternal ethnicities were different. Two cases were of Chinese ethnicity. A case-control study in Atlanta aimed to assess for a relationship between stress factors in mothers and conotruncal CHD. They found that maternal stress related to job loss, divorce, separation, or death and an unstable mental status increased the risk of conotruncal CHD (OR 2.4; 95%CI 1.42 to 4.2).[13] In our study, mothers with unstable mental status before and during pregnancy were excluded.

An Italian study aimed to determine pregnancy and birth outcomes after failure of oral contraceptives as an emergency contraceptive. The study was conducted from 2000 to 2003. Their results showed that levonorgestrel failure was not associated with increased risk of cardiac abnormalities.[14] However, a four-year study in Brazil showed that using misoprostol or oral contraceptives increased the risk of nervous system, musculosceletal, and cardiovascular disorders.[15] A prospective cohort study was conducted in Korea from March 2001 to June 2006. Subjects were women with a history of oral contraceptive use before and after 4 weeks' gestation. The results showed that oral contraceptive exposure did not increase congenital anomalies.[16] In our study, there was no association between maternal oral contraceptive

use before pregnancy and conotruncal CHD. We also assessed the duration of discontinuation of oral contraceptive use and duration of oral contraceptive exposure before pregnancy, and found no association with conotruncal CHD. Similarly, the Korean study showed that duration of oral contraceptive use, with low dose of progesterone (<0.75 mg), had no effect on the fetus.[16] Nor did an Italian study on long term oral contraceptive exposure, which found no increased risk of conotruncal CHD.[14] However, it has been reported that oral contraceptives containing high doses of progesterone have teratogenic effects, and a safe dose is not known.[16] The basic principles of teratology include timing of exposure, dose of the offending agent, and duration of the exposure.[17]

A limitation of our study was that the pregnancy history data was collected by interviews, which may have led to recall bias. Also, we were unable to match the case and control subjects. Further research is needed to assess the relationship between oral contraceptive use before pregnancy and conotruncal CHD.

In conclusion, we found that maternal oral contraceptive use before pregnancy does not increase the risk of conotruncal CHD.

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