ORIGINAL RESEARCH

Is maternal pre-pregnancy Body Mass Index associated with type of Congenital Heart Disease in offspring?

Nofita Fachryandini[1], Taufiq Hidayat[2]*, Ernawati[3], Mahrus A Rahman[2]
[1]Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[2]Department of Pediatric, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
[3]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

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***Corresponding author:**
Taufiq Hidayat
taufiq-h@fk.unair.ac.id

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ABSTRACT

Objectives: This study aimed to determine the association between maternal pre-pregnancy BMI and type of congenital heart disease (CHD) in offspring.
Materials and Methods: This retrospective cross-sectional study involved all mothers of children with CHD who visited Pediatric Outpatient Unit at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from January to December 2019. The maternal data were obtained from the KIA's (Maternal and Child Health) book or through anamnesis by telephone, while the offspring's data were collected from medical records. The data were analyzed using the Chi-Square test. Significance was determined at a 5% level ($p < 0.05$).
Results: We studied 117 mothers of children with CHD. The most frequent maternal pre-pregnancy body mass index (BMI) was normal (BMI 17-23 kg/m^2) accounting for 56.4% of the study population. The most common CHD was atrial septal defect (33.3%) among acyanotic patients and Tetralogy of Fallot (8.5%) among cyanotic patients. The Chi-Square test showed p=0.958 for the association between maternal pre-pregnancy BMI and type of CHD in offspring.
Conclusion: There was no association between maternal pre-pregnancy BMI and type of CHD in offspring.

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Highlights:

1. The most common CHD was atrial septal defect for acyanotic CHD and Tetralogy of Fallot for cyanotic CHD.
2. There was no association between maternal pre-pregnancy BMI and type of CHD in offspring.

INTRODUCTION

Congenital heart disease is the most common type of congenital disease, affecting 8.89 per 1000 live births and being the main cause of death in children with congenital abnormalities.[1] The cause of CHD remains unknown. In most cases, CHD is multifactorial and involves the combination of genetic and environmental factors. As many as 2-4% of CHD cases are associated with environmental factors such as pre-pregnancy obesity, diabetes mellitus, hypertension, phenyl-ketonuria, rubella, and cigarette smoking.[2]

The prevalence of overweight and obesity, measured from the Body Mass Index (BMI), has been a national health problem for several years. The latest data in 2018 from the Ministry of Health of the Republic of Indonesia showed that the prevalence of obesity in adults in Indonesia is 21.8%, whereas the prevalence of overweight is 13.6%.[3] Obesity and overweight have been associated with adverse pregnancy complications and outcomes, especially congenital heart disease.[4]

Previous studies have reported inconsistent results. Several studies have reported that mothers who are overweight or obese are at an increased risk of giving birth to a child with septal and conotruncal heart defect.[5,6] However, other studies reported that there might not be an association between maternal BMI and the likelihood of having a child with CHD.[7,8] Unfortunately, the association between maternal pre-pregnancy BMI and type of CHD in offspring among Indonesian pregnant women has not been studied. Hence, this study aims to determine the association between maternal pre-pregnancy BMI and type of CHD in offspring in Indonesia, so that appropriate changes in preventive health policies can be implemented.

MATERIALS AND METHODS

This was a retrospective cross-sectional study, conducted by collecting data from the medical record of the patients. The ethical approval for this study was obtained from the Regional Ethics Committee of Dr. Soetomo General Academic Hospital Surabaya, Indonesia (No.0103/KEPK/XI/2020). The population included all mothers of patients with congenital heart disease who visited the Pediatric Outpatient Unit, Dr. Soetomo Hospital, Surabaya, from January to December 2019. The sampling technique used in this study was a total sampling with inclusion and exclusion criteria. The inclusion criteria were mothers of patients with congenital heart disease who were recorded visiting the Pediatric Outpatient Unit, Dr. Soetomo General Hospital within the period of January to December 2019 and agreed to be a research subject by signing an informed consent. The exclusion criteria were the mothers of patients with congenital heart disease who have a family history of congenital heart disease and patients with incomplete medical record data. There were 326 patients who met the criteria.

The mothers were contacted via the telephone number listed in their medical records. Following an explanation of the study details, they were asked to provide consent and to confirm their agreement by signing an informed consent form. Some of the mothers did not agree to be the subject of the study due to several things, such as the patient had died, the telephone number was wrong, and they did not respond. So, 117 mothers agreed to be research subjects.

Mothers' data, such as weight, height, age, parity, history of abortion, pre-pregnancy diabetes, pre-pregnancy hypertension, were gathered from KIA's book or anamnesis through telephone, and offspring data such as sex, age, and type of CHD were gathered from medical records. Maternal pre-pregnancy BMI was calculated by weight and height recorded in the KIA book, usually measured in the first trimester. Weight gain in early pregnancy is generally very limited, with an average weight gain of 0.8-1.2 kg in the first trimester.[9] Thus, it can be said that maternal BMI in the first trimester represents pre-pregnancy BMI. In this study, we categorized BMI as underweight (BMI <17 kg/m^2), normal (BMI 17-23 kg/m^2), overweight (BMI 23-27 kg/m^2), and obesity (BMI >27 kg/m^2).[10] Data analysis used univariate analysis to describe the profile of pre-pregnancy mothers and children with CHD and bivariate analysis used SPSS software version 25 through the Chi-Square test. Statistical significance was defined as $p<0.05$.

RESULTS AND DISCUSSION

From January to December 2019, a total of 117 patients were studied. Table 1 shows the characteristics of the study sample. The most frequent maternal pre-pregnancy BMI was normal (66 mothers, 56.4%), the most frequent maternal pre-pregnancy age group was the age of 20-35 (83 patients, 70.9%), multipara (83 mothers, 70.9%) was more common than primipara, most mothers have never had a history of abortion (104 mothers, 88.9%) and the majority of mothers did not have pre-pregnancy diabetes mellitus (108 patients, 92.3%) and pre-pregnancy hypertension (114 patients, 97.4%). The dominant sex in congenital heart disease patients was male (63 patients, 53.8%), and the age group of patients was mostly 0-<5 years old (95 patients, 81.2%).

Table 1. Characteristics of the study sample

Characteristics	(n = 117)	%
Maternal Pre-Pregnancy BMI		
Underweight	5	4.3
Normal	66	56.4
Overweight	27	23.1
Obesity	19	16.2
Maternal Pre-Pregnancy Age (years)		
<20	3	2.6
20-35	83	70.9
>35	31	26.5
Parity		
Primipara	34	29.1
Multipara	83	70.9
History of Abortion		
Yes	13	11.1
No	104	88.9
Pre-Pregnancy Diabetes		
Yes	9	7.7
No	108	92.3
Pre-Pregnancy Hypertension		
Yes	3	2.6
No	114	97.4
Offspring Sex		
Male	63	53.8
Female	54	46.2
Offspring Age (years)		
0-<5	95	81.2
6-<11	15	12.8
11-18	7	6.0

Table 2. CHD's type of the patients

Type of CHD	n	%
Acyanotic	98	83.8
VSD	28	23.9
ASD	39	33.3
AVSD	7	6.0
PDA	17	14.5
PS	7	6.0
Cyanotic	19	16.2
ToF	10	8.5
TGA	2	1.7
Tricuspid atresia	1	1.0
PTA	2	1.7
EA	2	1.7
DORV	2	1.7
Total	117	100

Abbreviations: VSD: ventricular septal defect, ASD: atrial septal defect, AVSD: atrioventricular septal defect, PDA: patent ductus arteriosus, PS: pulmonary stenosis, ToF: Tetralogy of Fallot, TGA: transposition of the great arteries, PTA: persistent truncus arteriosus, EA: Ebstein's anomaly, DORV: double-outlet right ventricle

Table 2 shows the frequency of CHD type. Acyanotic CHD was more common (98 patients, 83.8%) than cyanotic CHD (19 patients, 16.2%). The most common acyanotic CHD's type was ASD (33.3%), VSD (23.9%), and PDA (14.5%), while the most common cyanotic CHD's type was ToF (8.5%).

Table 3. Characteristics by maternal pre-pregnancy BMI

Characteristics	Maternal Pre-Pregnancy BMI								p
	Underweight		Normal		Overweight		Obesity		
	n	%	n	%	n	%	n	%	
Maternal Pre-Pregnancy Age (years)									0.412
<20	0	0	3	2.6	0	0	0	0	
20-35	5	4.3	48	41.1	18	15.4	12	10.2	
>35	0	0	15	12.8	9	7.7	7	6.0	
Parity									0.060
Primipara	2	1.7	25	21.4	5	4.3	2	1.7	
Multipara	3	2.6	41	35.0	22	18.8	17	14.5	
History of Abortion									0.000
Yes	1	1.0	1	1.0	3	2.6	8	6.8	
No	4	3.4	65	55.4	24	20.5	11	9.4	
Pre-Pregnancy Diabetes									0.106
Yes	0	0	3	2.6	2	1.7	4	3.4	
No	5	4.3	63	53.8	25	21.4	15	12.8	
Pre-Pregnancy Hypertension									0.773
Yes	0	0	1	1.0	1	1.0	1	1.0	
No	5	4.3	65	55.4	26	22.2	18	15.4	
Offspring Sex									0.617
Male	2	1.7	39	33.3	13	11.1	9	7.7	
Female	3	2.6	27	23.1	14	11.9	10	8.5	
Offspring Age (years)									0.962
0-<5	4	3.4	53	45.3	23	19.6	15	12.8	
5-<11	1	1.0	9	7.7	2	1.7	3	2.6	
11-18	0	0	4	3.4	2	1.7	1	1.0	
Type of CHD									0.958
Acyanotic	5	4.3	56	47.7	17	14.5	16	13.7	
VSD	1	1.0	17	14.5	6	5.1	1	1.0	
ASD	3	2.6	24	20.5	8	6.8	7	6.0	
AVSD	0	0	4	3.4	1	1.0	2	1.7	
PDA	1	1.0	9	7.7	4	3.4	3	2.6	
PS	0	0	2	1.7	2	1.7	3	2.6	
Cyanotic	0	0	10	8.5	6	5.1	3	2.6	
ToF	0	0	5	4.3	2	1.7	3	2.6	
TGA	0	0	1	1.0	1	1.0	0	0	
Tricuspid atresia	0	0	1	1.0	0	0	0	0	
PTA	0	0	1	1.0	1	1.0	0	0	
EA	0	0	1	1.0	1	1.0	0	0	
DORV	0	0	1	1.0	1	1.0	0	0	

Table 3 illustrates that the mothers aged <20 years had normal pre-pregnancy BMI, while mothers aged 20-35 years tended to have normal pre-pregnancy BMI. Conversely, mothers aged >35 years were more likely to demonstrate pre-pregnancy overweight and obesity as defined by their BMI. Multiparas were more frequently found in all categories of BMI of pre-pregnancy mothers. Most of the mothers had no history of abortion in all categories of pre-pregnancy BMI. The majority of mothers had neither pre-pregnancy diabetes mellitus nor pre-pregnancy hypertension in all categories of pre-pregnancy BMI. The predominant sex of the child was male in each pre-pregnancy BMI category. The age of children was mostly found at the age of 0-<5 years in all categories of pre-pregnancy BMI. The most common defects found in all categories of BMI of pre-pregnancy mothers were ASD for acyanotic CHD and ToF for cyanotic CHD. There was no significant association between type of CHD (p=0.958), maternal age (p=0.412), parity (p=0.060), pre-pregnancy diabetes (p=0.106), pre-pregnancy hypertension (p=0.773), offspring sex (p=0.617), offspring age (p=0.962) and maternal pre-pregnancy BMI. However, we found a significant association between history of abortion and maternal pre-pregnancy BMI (p=0.000).

Congenital heart disease is the most common type of congenital disease and the main cause of death in children with congenital abnormalities. Obesity and overweight have been associated with adverse pregnancy complications and outcomes, especially congenital heart disease. However, this study did not find a significant association (p=0.958) between maternal pre-pregnancy BMI and type of CHD in offspring. Studies by Ghaderian et al. and Warrick et al. showed that maternal pre-pregnancy BMI had no significant association with the type of CHD in offspring.[7,8] Meanwhile, a study by Persson et al. showed a significant association between pre-pregnancy BMI level and aortic branch defect, ASD, and PDA in offspring.[5] Brite et al. demonstrated that maternal obesity levels were significantly associated with an increased risk of conotruncal defect, VSD, and ASD.[6] Zhang et al. also reported that maternal obesity tended to increase the risk of ASD and outflow tract defect in offspring.[11]

The mechanism for the association between maternal pre-pregnancy BMI and CHD remains unknown. However, several theories regarding the mechanism of higher risk of giving birth to a baby with congenital heart disease with increased BMI of pre-pregnancy mothers have been proposed. Increased fat mass, especially visceral fat mass, is associated with lipotoxicity and oxidative stress. Oxidative stress can arise from the intracellular accumulation of triacylglycerols (triglycerides), which impact mitochondrial efficiency, resulting in the accumulation of electrons in the electron transport chain that reacts with oxygen to form superoxide radicals. The combination of high lipid levels and oxidative stress leads to the production of three types of oxidized lipid products with harmful effects, namely lipid peroxides, oxidized lipoproteins (OxLDL), and oxysterols. Oxysterol can be toxic to cells which induces inflammation, oxidative stress, and apoptosis.[12] Oxidative stress stimulates Dnmt3b activity, which inhibits chromatin changes required for inducing Pax3 gene expression in the neuroepithelium. Inadequate expression of the Pax3 gene causes an increase in p53 protein levels resulting in increased apoptosis along the cardiac neural crest migration pathway, which results in disruption of cardiac neural crest migration, increases apoptosis along the cardiac neural crest migration pathway, and results in septal defects, outflow tract defects, and defects in cardiac arteries.[13,14]

Another possible theory is maternal diabetes. Diabetes is more common in overweight and obese individuals.[15] A recent meta-analysis by Najafi et al. reported a linear relationship between the risk of gestational diabetes mellitus (GDM) and an increase in maternal BMI.[16] Maternal diabetes inhibits the expression of the Pax3 gene in the neuroepithelium through hyperglycemia-induced oxidative stress. Inadequate expression of the Pax3 gene causes an increase in p53 protein levels resulting in increased apoptosis along the cardiac neural crest migration pathway.[13,14]

In addition to hyperglycemia, maternal malnutrition can also negatively affect embryogenesis. Mothers who are overweight or obese are more likely to be on a diet or have a poor diet. This can result in a lack of essential micronutrients such as folic acid and vitamin B12.[17] British guidelines suggested taking 5 mg folic acid supplementation per day for obese women.[18] Inadequate serum folate levels and vitamin B12 deficiency inhibit the re-methylation of 5-methyl-tetrahydrofolate, leading to an increase in homocysteine.[19] Excessive accumulation of homocysteine will result in disturbances in the migration, differentiation, and development of the cardiac neural crest, which is responsible for remodeling the great arteries, outflow septation, valvulogenesis, and development of the cardiac conduction system.[20,21]

Previous studies have identified that about 10% of CHD cases are associated with pathogenic mutations.[22,23] Meanwhile, epigenetic changes may be involved in the remaining cases. Catalano and Shankar also stated that maternal obesity could cause epigenetic changes in the embryo with an increased risk of cardiac malformations.[24] Epigenetic regulation can occur

through 3 mechanisms, the DNA methylation aberrations, histone modifications, and miRNA expression. These epigenetic changes have been found in several types of CHD in humans, the ASD, VSD, ToF, aortic stenosis, HLHS, and DORV. Epigenetic changes influence several processes in the formation and development of the heart, including differentiation and proliferation of cardiomyocytes, chamber morphogenesis, valve formation, and septation.[25]

The limitation of this study was that we could not examine the mothers directly, and our data were obtained from KIA's book and medical records. These may be inaccurate partly in measuring or recording data. Another limitation was that many missing patients were not included in our study, and we had no data of them and their mothers.

CONCLUSION

There is no association between maternal pre-pregnancy BMI and type of CHD in offspring from this study. We suggest that future studies consider a prospective study design to ensure more comprehensive data collection.

DISCLOSURES

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Conflict of interest

The author declares no conflict of interest

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Author Contribution

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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