CORRELATION BETWEEN MATERNAL AGE, LOW BIRTH WEIGHT, PREMATURITY AND HORMONAL DRUGS USING WITH THE OCCURRENCE OF HYPOSPADIAS (CASE STUDY AT BINA SEHAT JEMBER HOSPITAL, PARU JEMBER HOSPITAL, AND BHAYANGKARA BONDOWOSO HOSPITAL)

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ABSTRACT

Objective: *This research aims to determine the correlation between maternal age during pregnancy, low birth weight (LBW), prematurity, and history of hormonal drugs used in the first trimester of pregnancy with the occurrence of hypospadias.* ***Material & Methods:*** *This research is an observational analytic research with case control design. The sample in this study were 50 samples that consisting of 25 patients with hypospadias and 25 patients without hypospadias at Bina Sehat Jember Hospital, Paru Jember Hospital, and Bhayangkara Bondowoso Hospital. After determined every case and control group, data acquired retrospectively by traced the hypospadias risk factors (maternal age at pregnancy, LBW, prematurity, and history of hormonal drugs using in the first trimester of pregnancy) by interviewing the patient's mother. The data of this research were analyzed by bivariate and multivariate using SPSS 16.0. Bivariate analysis in this study used chi-square Yates correction (chi-square with continuity correction) and fisher's exact test, whereas multivariate analysis used logistic regression techniques with significance p-value<0.05.* ***Results:*** *The result of bivariate analysis in this study showed that variable maternal age during pregnancy more than 35 years (p = 0.667) has no correlation with occurrence of hypospadias, while variable of LBW (p = 0.027), prematurity (p = 0.041), and the history of hormonal drug use in the first trimester of pregnancy (p = 0.049) have a correlation with the occurrence of hypospadias.* ***Conclusion:*** *In this study, there was a significant correlation between LBW, prematurity, and history of hormonal drugs using in the first trimester of pregnancy with the occurrence of hypospadias. This study did not show a significant correlation between maternal age during pregnancy with the occurrence of hypospadias.*

Keywords: *Hypospadias, maternal age, LBW, prematurity, hormonal drugs.*

ABSTRAK

Tujuan: *Mengetahui hubungan antara usia ibu saat hamil, berat badan lahir rendah (BBLR), prematuritas, dan riwayat penggunaan obat hormonal pada kehamilan trimester pertama dengan kejadian hispospadia.* ***Bahan & Cara:*** *Penelitian ini merupakan penelitian observasional analitik dengan desain case control. Sampel dalam penelitian ini sebanyak 50 sampel yang terdiri dari 25 pasien hipospadia dan 25 pasien tanpa hipospadia di RS Bina Sehat Jember, RS Paru Jember, dan RS Bhayangkara Bondowoso. Setelah ditentukan setiap kasus dan kelompok control, data diperoleh secara retrospektif dengan menelusuri factor resiko hipospadia (usia ibu saat hamil, BBLR, prematuritas, dan riwayat penggunaan obat hormonal pada trimester pertama kehamilan) dengan mewawancarai ibu pasien. Data penelitian ini dianalisis secara bivariate dan multivariate menggunakan SPSS 16.0. Analisis bivariate dalam penelitian ini menggunakan koreksi Chi-square Yates (Chi-square dengan koreksi kontinuitas) dan Fisher's Exact Test, sedangkan analisis multivariate menggunakan teknik regresi losgistik dengan nilai signifikansi p<0.05.* ***Hasil:*** *Hasil analisis bivariat dalam penelitian ini menunjukkan bahwa variable usia ibu hamil lebih dari 35 tahun (p=0.0667) tidak memiliki hubungan dengan kejadian hipospadia, sedangkan variable BBLR (p=0.027), prematuritas (p=0.041), dan riwayat penggunaan obat hormonal pada kehamilan trimester pertama (p=0.049) memiliki hubungan dengan terjadinya hipospadia.* ***Simpulan:*** *Pada penelitian ini terdapat hubungan yang bermakna anatara BBLR, prematuritas dan riwayat penggunaan obat hormonal pada kehamilan trimester I dengan kejadian hipospadia. Penelitian ini tidak menunjukkan adanya hubungan yang bermakna antara usia ibu saat hamil dengan terjadinya hipospadia.*

Kata Kunci: *Hipospadia, usia ibu, BBLR, prematuritas, obat hormonal.*

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INTRODUCTION

Hypospadias is a congenital malformation that occurs in boys where the external urethral meatus is located more proximally in the ventral side of the penis, whereas normally located at the tip of the penis.[1] Hypospadias occur because an incomplete fusion of the urethral folds, but until now the etiology of hypospadias is unknown with certainty.[1-2] The etiology of hypospadias thought to be multifactorial in terms of genetic, endocrine, and environmental factors.[3]

Hypospadias may occur due to several factors, such as maternal age, low birth weight (LBW), prematurity, and history of hormonal drugs used in the first trimester of pregnancy.[4-9] Many studies have suggested that hypospadias are associated with placental insufficiency, which can reduce the supply of nutrients and gonadotropin to the fetus which may affect the occurrence of hypospadias.[4] Placental insufficiency leads to a lack of nutrients that inhibit fetal growth and reduce human chorionic gonadotropin (HCG) production which can affect androgen synthesis.[10-11]

The closure of the urethral fold is affected by the androgen hormone. The use of antiandrogenic drugs is thought to increase the risk of hypospadias.[12] Androgens and estrogens play an important role during the development of the genitalia and the presence of hormonal imbalances during embryogenesis can cause congenital abnormalities such as hypospadias.[13] One of the synthetic estrogen is diethylstilbestrol (DES) used in pregnant women which aims to prevent miscarriage, premature delivery, and complications related to pregnancy.[14] Some studies have reported that the use of estrogen and progestin may increase the risk of hypospadias.[7-9]

OBJECTIVE

To determine the correlation between maternal age during pregnancy, LBW, prematurity, and history of hormonal drugs using in the first trimester of pregnancy with the occurrence of hypospadias.

MATERIAL & METHODS

This research is observational analytic research with case-control design. The inclusion criteria of sample in this research are (1) case groups were patients with hypospadias diagnosis and control group were patients without hypospadias diagnosis; (2) patients aged 0-18 years; (3) patients take medication at Bina Sehat Jember Hospital, Paru Jember Hospital, and Bhayangkara Bondowoso Hospital from October 2015-2017; and (4) willing to participate in this research. Whereas, the exclusion criteria is patients with data required in this study were incomplete.

After determined every case and control group, data was acquired retrospectively by traced the hypospadias risk factors (maternal age at pregnancy, LBW, prematurity, and history of hormonal drugs using in the first trimester of pregnancy) by interviewing the patient's mother. This research has received permission of ethical clearance from the ethics committee of the Faculty of Medicine, University of Jember.

The data of this research were analyzed by bivariate and multivariate using SPSS 16.0. Bivariate analysis in this study used chi-square Yates correction (chi-square with continuity correction) and fisher's exact test, whereas multivariate analysis used logistic regression techniques with significance p-value<0,05.

RESULTS

The sample in this study were 50 samples that consisting of 25 patients with hypospadias and 25 patients without hypospadias. The results of this study showed that the most hypospadias type is posterior type which is 14 (56%) cases (Table 1). The result of bivariate analysis in this study showed that maternal age during pregnancy more than 35 years ($p = 0.667$) has no correlation with the occurrence of hypospadias, while LBW ($p = 0.027$), prematurity ($p = 0.041$), and the history of hormonal drugs using in the first trimester of pregnancy ($p = 0.049$) have a correlation with the occurrence of hypospadias. In this study LBW may increase the risk of hypospadias by 5.7 times, prematurity may increase the risk of hypospadias by 6.4 times, and hormonal drugs using in the first trimester of pregnancy also increase the risk of hypospadias by 9.3 times (Table 2).

The result of logistic regression analysis showed that the most potential variables for the occurrence of hypospadias from the largest to the smallest were LBW ($p = 0.010$; OR = 0.139) and the history of hormonal drugs using in the first trimester of pregnancy ($p = 0.028$; OR = 0.080) (Table 3).

Table 1. Characteristic of research subjects.

Variables		The occurrence of hypospadias			
		Hypospadias		Without hypospadias	
		N	%	N	%
Hypospadias	Anterior	4	16	-	-
	Middle	7	28	-	-
	Posterior	14	56	-	-
Maternal age during pregnancy	>35 years	2	33.3	4	66.7
	≤35 years	23	52.3	21	47.7
Low birth weight	<2500 grams	11	78.6	3	21.4
	≥2500 grams	14	38.9	22	61.1
Prematurity	<37 weeks	9	81.8	2	18.2
	≥37 weeks	16	41.0	23	59.0
The history of hormonal drugs using in the first trimester of pregnancy	Ever	7	87.5	1	12.5
	Never	18	42.9	24	57.1

Table 2. The result of bivariate analysis between various variables with occurrence of hypospadias.

Variables	P-value	OR (CI 95%)
Maternal age during pregnancy	0.667*	0.457 (0.076-2.755)
Low birth weight	0.027	5.762 (1.363-24.262)
Prematurity	0.041	6.469 (1.230-34.012)
The history of hormonal drugs using in the first trimester of pregnancy	0.049*	9.333 (1.052-82.780)

** fisher's exact test*

Table 3. The result of logistic regression analysis

Variables	P-value	OR (CI 95%)
Low birth weight	0.010	0.139 (0.031-0.626)
The history of hormonal drugs using in the first trimester of pregnancy	0.028	0.080 (0.008-0.760)

DISCUSSION

The results of this research indicate that the maternal age during pregnancy more than 35 years has a significance p-value = 0.667 which means there is no correlation between maternal age during pregnancy more than 35 years with the occurrence of hypospadias. This study is corresponding with previous studies which state that maternal age at pregnancy more than 35 years is not associated with occurrence of hypospadias.[5,8,15] Previous studies have suggested that maternal age during pregnancy has a role in the occurrence of hypospadias.[4,6,10] This is because mothers who pregnant at the age more than 35 years have a risk of placental insufficiency and poor placental blood flow.[16] Placental insufficiency that occurs leads to inadequate provision of human chorionic gonadotropin (HCG) of the fetus thus reducing the stimulation of fetal testicular steroidogenesis that may affect fetal androgen. This may affect the development of male genitalia.[8]

The results of this study indicate that there is a correlation between LBW with the occurrence of hypospadias with significance p-value = 0.027. This study is in line with previous studies which state that LBW is associated with occurrence of hypospadias.[5-6] The results of this study found that LBW i.e weight at birth less than 2500 grams will be increase occurrence of hypospadias 5.7 times. The result of this study stated that there is correlation between

prematurity with occurrence of hypospadias with significance p-value = 0.041. This research was supported by several studies that explain that prematurity has a correlation with occurrence of hypospadias.[5,6,8] In this study, prematurity ie birth at gestational age less than 37 weeks will be increase occurrence of hypospadias 6.4 times.

Low birth weight and prematurity are associated with the occurrence of hypospadias thought to be due to placental insufficiency, which is associated with impaired growth and development of intrauterine.[17] Placental insufficiency may interfere with the delivery of nutrients and HCG to the fetus which may reduce the stimulation of fetal testicular steroidogenesis thus affecting fetal androgen.[8] The presence of disturbances in prolonged androgen pathways may affect the development of male genitalia resulting in hypospadias.[17]

Using hormonal drugs in the first trimester of pregnancy either estrogen, progesterone, or combination of both have a association with the occurrence of hypospadias. The result of this study stated that there is correlation between hormonal drug using in the first trimester of pregnancy with occurrence of hypospadias with significance p-value = 0.049. The results of this study are in tune with previous research which states that there is a significant relationship between exposure to diethylstilbestrol (DES) with the occurrence of hypospadias.[7] Another research also stated that boys exposed to DES during pregnancy had a 21.3 times greater risk of hypospadias.[18] In addition, other studies about progestin used by pregnant women in early pregnancy to prevent complications of pregnancy or miscarriage have a 3.9 times greater risk of having a child with hypospadias.[9] In this study, hormonal drugs using in the first trimester of pregnancy will be increase occurrence of hypospadias 9.3 times.

The use of DES in the first trimester of pregnancy can lead to disturbance of androgen and estrogen balance in the fetus because DES has an estrogenic and antiandrogenic role by competing with androgens by binding to androgen receptors.[7] Increased exposure to estrogen in the uterus may lead to decreased development of Leydig cells, inhibiting testosterone production or receptor androgen expression in order to increase the risk of hypospadias.[19] Whereas the exposure of progestins may inhibit steroid-5α-reductase which is a key enzyme in the sexual differentiation of men, thereby reducing the conversion of testosterone to dihydrotestosterone (DHT) that required in the formation and development of the genitalia of men, it's can increase the risk of hypospadias.[9,20]

CONCLUSION

Many factors affect the occurrence of hypospadias. In this study, there were a significant correlation between LBW, prematurity, and history of hormonal drugs using in the first trimester of pregnancy with the occurrence of hypospadias. This study did not show a significant correlation between maternal age during pregnancy with the occurrence of hypospadias.

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