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Neonatal outcomes in *in vitro* fertilization (IVF) pregnancies

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ABSTRACT

In vitro fertilization (IVF) has been associated with poor neonatal outcomes. Preterm birth, small-for-gestational age (SGA), and low birth weight (LBW) rates are approximately twice as high in IVF pregnancies than in natural pregnancies. The IVF procedures have become more routine in recent years in Indonesia, but there have been few assessments of neonatal outcomes. The study aimed to evaluate the risk of preterm birth, SGA, and LBW in IVF infants. This was a retrospective cohort study performed in Dr. Sardjito General Hospital, Yogyakarta from January 2012 to December 2016. Pre-coded questionnaires were used to collect data from medical records. The relative risk of preterm birth, SGA, and LBW among IVF infants were calculated and compared to naturally conceived infants. A total sampling method was used for the IVF infants and a simple random sampling method was used for naturally conceived infants, who were born on the same day as an infant in the IVF group.

A total of 108 infants were recruited, consisting of 54 IVF infants and 54 naturally conceived infants. The IVF infants had increased risk of preterm birth (RR = 2.0; 95%CI 0.52 - 7.58) and LBW (RR = 1.25; 95%CI 0.53 - 2.92). However, the IVF infants did not have an increased risk of SGA (RR = 1.0; 95%CI 0.21 - 4.73). In conclusion, the risk of preterm birth and LBW in IVF infants are higher than in naturally conceived infants, but not statistically significant. However, there is no increased risk of SGA in IVF infants.

ABSTRAK

Fertilisasi *in vitro* (FIV) dihubungkan dengan luaran neonatus yang rendah. Tingkat kelahiran preterm, bayi kecil untuk usia kehamilan, berat badan lahir rendah sekitar dua kali lebih tinggi pada kehamilan FIV dibandingkan kehamilan normal. Teknik FIV telah rutin dilakukan di Indonesia beberapa tahun belakangan ini, tetapi sedikit dilakukan penilaian terhadap luaran neonatusnya. Penelitian ini dilakukan bertujuan untuk mengkaji risiko kelahiran preterm, bayi kecil untuk usia kehamilan, berat badan lahir rendah pada anak dengan FIV. Penelitian ini merupakan penelitian kohort retrospektif yang dilakukan di RSUP Dr. Sardjito, Yogyakarta dari Januari 2012 sampai Desember 2016. Kuesioner berkode digunakan untuk mengumpulkan data dari rekam medik. Risiko relatif kelahiran preterm, bayi kecil untuk usia kehamilan, berat badan lahir rendah dihitung dan dibandingkan dengan bayi lahir normal. Metode sampling total digunakan untuk bayi dengan FIV dan metode sampling acak sederhana digunakan untuk bayi normal yang lahir pada hari yang sama. Total sebanyak 108 bayi direkrut yang terdiri dari 54 bayi dengan FIV dan 54 bayi normal. Fertilisasi *in vitro* meningkatkan risiko kelahiran preterm (RR = 2,0; 95%CI 0,52 - 7,58) dan berat badan lahir rendah (RR = 1,25; 95%CI 0,53 - 2,92). Namun demikian,

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FIV tidak mempunyai risiko bayi kecil untuk usia kehamilan (RR = 1,0; 95%CI 0,21-4,73). Dapat disimpulkan, risiko kelahiran preterm dan berat badan lahir rendah pada FIV lebih tinggi daripada bayi normal, tetapi tidak berbeda nyata. Namun demikian, tidak ada kenaikan risiko terjadinya bayi kecil untuk usia kehamilan.

Keywords: *in vitro* fertilization – preterm - small for gestational age - low birth weight – relative risk

INTRODUCTION

In vitro fertilization (IVF) is one of several assisted reproductive technologies (ART). The number of babies conceived through this procedure is increasing, with an estimated 3-5 million IVF babies worldwide.¹⁻³ As the number of newborns increase, several studies have been conducted to evaluate neonatal outcomes of low birth weight (LBW), preterm birth, and small-for-gestational age (SGA). These outcomes occur almost twice as often compared to natural pregnancies, even in singleton IVF pregnancies.⁴⁻⁷ Guidelines provided, to optimize obstetrical management and counselling (counseling) of Canadian women using ART, and to identify areas specific to birth outcomes and ART requiring further research. Perinatal outcomes of ART pregnancies in subfertile women are compared with those of spontaneously conceived pregnancies. Perinatal outcomes are compared between different types of ART. This guideline discusses the adverse outcomes that have been recorded in association with ART, including obstetrical complications, adverse perinatal outcomes, multiple gestations, structural congenital abnormalities, chromosomal abnormalities, imprinting disorders, and childhood cancer. The Cochrane Library and MEDLINE were searched for English-language articles from 1990 to February 2005, relating to assisted reproduction and perinatal outcomes. Search terms included assisted reproduction, assisted reproductive technology, ovulation induction,

intracytoplasmic sperm injection (ICSI). Studies in Taiwan and India reported that the prevalence of preterm birth was increased in IVF pregnancies compared to natural pregnancies.^{8,9}

A study in eight infertility centers in Indonesia showed a pregnancy success rate of 29.46%.¹⁰ In 2014, the IVF program at Dr. Sardjito General Hospital, Yogyakarta, had a 25.4% pregnancy success rate, while the percentage of live births was 19.8%. These percentages increased in 2015 to 30.9% and 25.1%, respectively.^{11,12} The IVF program in Indonesia has existed for approximately 29 years with an increasing percentage of live births, but the data on neonatal outcomes remains unclear. Hence, this study aimed to evaluate the risk of poor neonatal outcomes in IVF infants.

MATERIALS AND METHODS

Subjects

This retrospective cohort study was done from January 2012 to December 2016. Infants who were born at Dr. Sardjito General Hospital, Yogyakarta, through IVF pregnancies (IVF group) and natural pregnancies (natural group) were recruited as subjects. The infants whose mothers underwent IVF procedures outside this hospital and those whose medical records were not found or incomplete were excluded. The data were collected from medical records using questionnaires.

Protocol of study

A total sampling method for IVF infants and a simple random sampling method for the natural group were used. Naturally conceived infants born on the same day as an IVF infant underwent simple random sampling for inclusion. If no naturally conceived infant was found on the same day as an IVF infant, retrieval was extended to up to three days later.

A minimum of 64 subjects was required for each group to obtain 90% power with 5% significance level. In this study, dependent variables were neonatal outcomes, i.e., birth weight, gestational age, and birth weight according to gestational age, while independent variables were the process of fertilization (IVF/natural). Confounding variables were maternal age, parity, and placental abnormalities.

The definition of LBW was weight at birth of less than 2,500 g, regardless of the gestational age; the definition of SGA was birth weight according to gestational age of less than 10th percentile on the Lubchenco curve. Gestational age was defined as the length of pregnancy until the time of delivery. By the Dubowitz score, preterm was defined as <37 weeks gestational age.¹³ Maternal age was defined as the age of the mother at the time of delivery. Parity was defined as the number of previous pregnancies that reached viable gestational age. Placental abnormalities included placental abruptio or placenta previa. Faculty of Medicine, Universitas , Yogyakarta

Statistical analysis

Statistical analysis was done using SPSS Statistics 20. Univariate analysis was performed on numerical data and was shown as mean or median, while categorical data was displayed in proportion. Chi-square or Fisher’s exact tests were used to compare independent and dependent variables, with relative risk as a measure of the strength of

the relationship. Statistical significance was defined to be $p < 0.05$. Multivariate analysis was performed using logistic regression.

RESULTS

Fifty-eight IVF infants were initially screened for this study, but three infants were excluded due to their IVF not having been performed in Dr. Sardjito General Hospital and one due to loss of the medical records. Hence, 54 subjects were included in the IVF group. No infants born from natural pregnancies were excluded, for a total of 54 naturally conceived subjects (FIGURE 1).

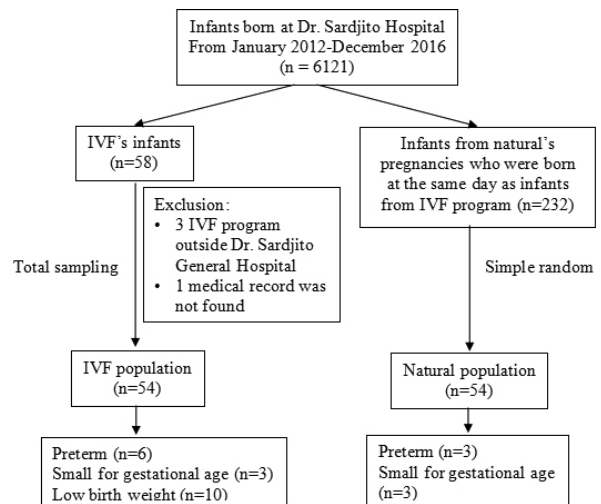


FIGURE 1. Flowchart of subjects recruitment

The characteristics of subjects are shown in TABLE 1. The IVF group (88.9%) had a greater proportion of parity 0 (nulliparous) than the natural group (38.9%). In addition, the IVF group (22.2%) had a greater proportion of multiple pregnancies than the natural group (7.40%), though the proportion of singletons (77.8%) was still greater than the proportion of multiples (22.2%) in the IVF group. Moreover, the IVF group (92.6%) had a greater proportion of caesarean section deliveries than the natural group (48.1%).

TABLE 1. Characteristics of IVF and naturally conceived subjects

Characteristics	IVF (n = 54)	Natural (n = 54)
Maternal age [n (%)]		
• 20-34 years	34 (63.0)	36 (66.7)
• ≥35 years	20 (37.0)	18 (33.3)
Maternal age (mean ± SD years)	33.2 ± 3.74	31.4 ± 5.53
Parity prior to this pregnancy [n (%)]		
• 0	48 (88.9)	21 (38.9)
• ≥1	6 (11.1)	33 (61.1)
Gestational age, n (%)		
• Full term	48 (88.9)	51 (94.4)
• Preterm	6 (11.1)	3 (5.60)
Number of fetuses [n (%)]		
• Single	42 (77.8)	50 (92.6)
• Multiple	12 (22.2)	4 (7.40)
Sex [n (%)]		
• Male	27 (50.0)	34 (63.0)
• Female	27 (50.0)	20 (37.0)
Birth weight, n (%)		
• Normal	44 (81.5)	46 (85.2)
• Low	10 (18.5)	8 (14.8)
Birth weight [median (min-max)/mean (SD)]	2,875.0 (600-3850)	2,928.4 (400)
Birth weight for gestational age, n (%)		
• AGA	51 (94.4)	51 (94.4)
• SGA	3 (5.60)	3 (5.60)
Mode of delivery [n (%)]		
• Vaginal	4 (7.4)	28 (51.9)
• Caesarean section	50 (92.6)	26 (48.1)
Placental abnormalities, n (%)	4 (7.4)	0 (0)

AGA=appropriate for gestational age; SGA=small for gestational age

TABLE 2 shows the bivariate analysis between the independent variables and preterm. The IVF infants had two times the risk of preterm birth than natural infants. However, it was not significantly different (95%CI 0.52-

7.58; p=0.48). Other independent variables such as maternal age, parity, and placental abnormalities had no significantly association with the occurrence of preterm birth (p>0.05).

TABLE 2. Bivariate analysis of independent variables and preterm

Variables	Preterm (n=9)	Full term (n=99)	RR	Bivariate 95% CI	p
Fertilization process [n (%)]					
• IVF	6 (11.1)	48 (88.9)	2.0	0.52-7.58	0.48
• Natural	3 (5.6)	51 (94.4)			
Maternal age [n (%)]					
• 20-34 years	5 (7.1)	65 (92.9)	0.67	0.19-2.37	0.71
• ≥35 years	4 (10.5)	34 (89.5)			
Parity prior to pregnancy [n (%)]					
• Nulliparous	6 (8.7)	63 (91.3)	1.13	0.29-4.27	1.00
• Multiparous	3 (7.7)	36 (92.3)			
Placental abnormalities [n (%)]					
• Yes	1 (25)	3 (75)	3.25	0.52-20.1	0.29
• No	8 (7.7)	96 (92.3)			

Bivariate analysis of the independent variables and SGA revealed no increased risk of SGA in IVF infants (RR=1.0; 95%CI 0.21- 4.73; p=1.0). Other independent

variables such as maternal age, parity, and placental abnormalities also had no significant association with the incidence of SGA (TABLE 3).

TABLE 3. Bivariate analysis of independent variables and SGA

Variable	SGA (n=6)	AGA (n=102)	RR	Bivariate 95%CI	p
Fertilization process [n (%)]					
• IVF	3 (5.6)	51 (94.4)	1.0	0.21- 4.73	1.0
• Natural	3 (5.6)	51 (94.4)			
Maternal age [n (%)]					
• 20-34 years	3 (4.3)	67 (95.7)	0.54	0.11- 2.56	0.66
• ≥35 years	3 (7.9)	35 (92.1)			
Parity prior to this pregnancy [n (%)]					
• Nulliparous	3 (4.3)	66 (95.7)	0.56	0.12- 2.67	0.66
• Multiparous	3 (7.7)	36 (92.3)			
Placenta abnormalities [n (%)]					
• Yes	0 (0)	4 (100)			1.00
• No	6 (5.80)	98 (94.2)			

SGA=small for gestational age; AGA=appropriate for gestational age

Bivariate analysis of the independent variables and LBW revealed that IVF infants had 1.2 times higher risk of LBW compared to naturally conceived infants. However, it was not significantly different (95%CI 0.53

- 2.92; p= 0.6). Other independent variables such as maternal age, parity, and placental abnormalities were not also significantly associated with LBW incidence (TABLE 4).

TABLE 4. Bivariate analysis of independent variables and LBW

Variable	LBW (n=18)	NBW (n=90)	RR	Bivariate 95%CI	p
Fertilization process [n (%)]					
• IVF	10 (18.5)	44 (81.5)	1.25	0.53- 2.92	0.60
• Natural	8 (14.8)	46 (85.2)			
Maternal age [n (%)]					
• 20-34 years	10 (14.3)	60 (85.7)	0.67	0.29 -1.57	0.37
• ≥35 years	8 (21.1)	30 (78.9)			
Parity prior to pregnancy [n (%)]					
• Nulliparous	11 (15.9)	58 (84.1)	0.88	0.37 -2.10	0.78
• Multiparous	7 (17.9)	32 (82.1)			
Placenta abnormalities [n (%)]					
• Yes	1 (25)	3 (75)	1.53	0.26- 8.82	0.52
• No	17 (16.3)	87 (83.7)			

LBW: low birth weight; NBW: normal birth weight

Multivariate analysis could not be performed in this study due to no variables had p values <0.25 after bivariate analysis performed.

DISCUSSION

The proportions of preterm infants were 11.1% and 5.6% in the IVF and natural groups, respectively. Similarly, a previous study reported that the prevalence of preterm ranged from 7.8 to 16.1% in IVF population and 4.5% to 8.0% in natural population.¹⁴ Nevertheless, no significant association between IVF and preterm (p=0.48) was observed, whereas several previous studies showed significant results.^{14,15} Koivurova *et al.*¹⁶ found no significant association between singleton IVF and preterm (OR 1.5; 95%CI 0.7 - 3.2), in which the control was only singleton pregnancies taken from the general population. However, this result became significant when both singleton and multiple pregnancies were taken as control subjects (OR 5.6; 95%CI 3.7 - 8.6). As such, sample diversity is an important factor in the incidence of preterm.¹⁶

All infants from ART procedures may be predisposed to preterm birth. Previous studies divided ART into subgroups, i.e., fresh with frozen embryos, oocyte donors with own oocytes, standard IVF with intracytoplasmic sperm injection (ICSI), and third day with fifth day embryo showed greater risk of preterm, LBW and VLBW in each subgroup.^{17,18} Maternal morbidity and mortality among Swedish women giving birth after in vitro fertilisation (IVF) However, Romundstad *et al.*¹⁹ also compared natural conception with ART in the same mothers and found no significant difference. They concluded that ART did not harm the perinatal outcome, but genetics was more likely to be an underlying factor of preterm incidence. Another study mentioned that ART pregnancies were generally more closely monitored, such that birth was more frequently subject to induction and caesarean section. These ART interventions also have been associated with SGA incidence, increased perinatal mortality, and VLBW.¹⁴

The proportion of SGA in our study was similar in both the IVF and natural groups

(5.6%). Previous studies reported SGA in 12.7% of IVF pregnancies and 13% of natural pregnancies,²⁰ and 2.89% in both IVF and natural newborns.²¹ In this study, there was no increased risk of SGA in IVF infants. However, this finding may not be conclusive, as a previous meta-analysis stated that the risk of SGA in IVF pregnancies was 1.3 times higher compared to natural pregnancies (95%CI 1.27 to 1.53).²² In contrast, other studies stated that there was no increased risk of SGA in IVF infants.^{20,21,23} Wen *et al.*²³ noted that general and more diverse populations tended to have significant influences on SGA incidence.

The proportions of LBW in our study were 18.5% and 14.8% in the IVF and natural groups, respectively. Similarly, a previous study reported LBW of 11.2% in IVF and 11.6% in natural newborns.²⁰ Our bivariate analysis revealed no significant association between IVF and LBW incidence ($p=0.60$), similar to previous studies that compared LBW and preterm in ART and non-ART groups.^{20,24} In contrast, a recent meta-analysis suggested that LBW tended to occur in the IVF population compared to the natural population, even if the baby is full term.²⁵ Differences in the size of the research scale may explain our lack of association between IVF and LBW, as small-scale research tended to get no significant results.²⁰

Placental abnormalities (all placenta previa) were only found in our IVF group (7.4%), but there were not significantly different from the natural population. IVF procedures such as cervical catheterization, or mechanically- inducing uterine contractions may play a major role in implantation in the lower uterine segment, thus leading to placenta previa.¹⁹ Another study explained that high concentrations of estradiol hormone in the IVF cycle increased complications associated with placental aberration by affecting endometrial

growth and decidualization.²⁶

Several previous studies have noted that the underlying factors of preterm, SGA, and LBW remain unclear.^{7,27,28} To date, the underlying factors are maternal age, infertility/subfertility, genetics, as well as the IVF technique itself, but we were unable to assess for these variables in our study. Furthermore, women who undergo ART may differ from the general population, as these women usually have high socioeconomic status, good nutritional status, better antenatal care, and sufficient rest during pregnancy. These factors are believed to positively affect pregnancy and its outcome.²⁴ Another study reported that most pregnancies from the IVF program had no complications and resulted in the birth of healthy babies.²⁹

Several limitations of our study should be noted. The small and potentially inadequate sample size as well as the retrospective study design may have led to information bias. The selection of no intervention populations (natural populations) appropriate to the IVF population WAS also a weakness. Women who underwent IVF treatment in this study generally had middle to upper economic status (because the IVF program in Indonesia is not guaranteed by insurance), more routine control, consultation, and treatment during pregnancy, especially by the obstetrician. Hence, the IVF group may have received better attention and care than the natural group. Another weakness in our study was that some important variables such as socioeconomic status and maternal education were not recorded completely in the medical records, so they were not included in the analysis.

CONCLUSION

In conclusion, the risk of preterm birth and LBW in IVF infants tend to be higher than

in naturally conceived infants. However, they are not statistically significant. In addition, there is no increased risk of SGA in IVF infants. Further research using a larger sample size is needed for more representative data of the actual conditions in the population.

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