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Original Article

Neonatal outcomes from in vitro fertilization-conceived pregnancies

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Abstract

Background *In vitro* fertilization (IVF) shows potential to improve pregnancy success, especially for infertile couples. This technique has some risks for neonates in the perinatal period and may affect their future health.

Objective To investigate the characteristics and clinical outcomes of neonates from IVF-conceived pregnancies.

Methods This retrospective study was conducted in neonates from IVF-conceived pregnancies at Bunda Women's and Children's Hospital, Jakarta. We gathered data from medical records about maternal age and morbidity, gravidity, gestational age, method of delivery, multiple gestation, also neonates' significant profiles like prematurity, birth weight, Apgar score, and morbidities in perinatal period.

Results There were 361 neonates whose mothers underwent IVF included in this study. Most mothers were ≤35 years (70.9%) and on their first pregnancy (69.2%). Maternal complicating factors were premature contractions (16.6%), premature rupture of membranes (8.3%), and twin pregnancy (31.5%). About 98.6% of deliveries were performed by caesarean section and 61.2% neonates were born at full term gestation. Preterm deliveries occurred at a mean gestational age of 34.4 (SD 2.4) weeks. Subjects' mean birth weight was 2,800.2 (SD 640.3) grams, with 26.3% in the low-birth-weight category. Most neonates (93.0%) were appropriate weight for gestational age and had good Apgar scores in the first minute (92.2%) and fifth minute (99.7%). However, 24.3% of neonates needed intensive care (NICU) with morbidities. The longest length of NICU stay was 100 days, with mortality of 7.9% of NICU-treated infants.

Conclusion In our setting, most neonates from the IVF program are born with good outcomes, although preterm birth rate, low birth weight, need for NICU care, and mortality rate are quite high. Further study is needed to evaluate long-term outcomes of IVF neonates. **[Paediatr Indones. 2023;63:238-44; DOI: https://doi.org/10.14238/pi63.4.2023.238-44**].

Keywords: *neonates; in vitro fertilization; outcomes; preterm births; low birth weights*

In vitro fertilization (IVF) is an assisted reproductive technology (ART) that has been widely chosen as a therapeutic modality for infertile couples. This technique involves stimulation of the ovaries by gonadotropin hormone, followed by oocyte retrieval using a sedative procedure, fertilization by sperm in the laboratory, embryo development, and finally, transfer of the embryo into the uterus.[1,2] The number of neonates born through this process continues to increase, with an estimated 3-5 million IVF neonates worldwide since the first successful IVF and embryo transfer was reported in 1978.[3,4]

In accordance with reports of success, IVF also poses potential risks for both mother and baby.[5] In most ARTs, higher numbers of embryos are transferred to the uterus, resulting in multiple pregnancies. This problem leads to high risk of maternal Cesarean section, preterm delivery, perinatal bleeding, hypertension in pregnancy, and gestational diabetes. The risk to neonates includes prematurity, low birth weight (LBW), small gestational age (SGA),

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birth defects, and death.[5-8] Despite advanced medical services in perinatal and neonatal care, neonates with low birth weight (LBW) still have a risk of poor outcomes, along with a socioeconomic burden, especially for parents having premature neonates who require NICU treatment.[2,9]

The IVF program in Indonesia has existed for approximately 30 years, with the percentage of live births continuing to increase,4 but data on neonatal outcomes is lacking. Therefore, we aimed to report on the characteristics and clinical outcomes of neonates from the IVF program at *Rumah Sakit Ibu dan Anak Bunda* (Bunda Women's and Children's Hospital), Jakarta, from January to December 2021.

Methods

This retrospective study was conducted in Bunda Women's and Children's Hospital, Jakarta. Subjects were selected by total sampling in the NICU and routine neonatal care ward from January to December 2021. Neonates from IVF-conceived pregnancies and delivered at Bunda Women's and Children's Hospital were included in this study. Medical record data during the observation period were recorded including demographic information, clinical data, and outcomes. Exclusion criteria were incomplete medical records or newborns who were referred to another hospital.

Prematurity was defined as neonates under 37 weeks' gestation, and subclassified according to the *World Health Organizatio*n (WHO).[10] Birth weight below the normal value was subcategorized into three groups.[11] Lubchenco charts were used to determine birth weight categories according to gestational age.[12] Diagnoses of respiratory distress syndrome (RDS) or neonatal respiratory distress syndrome were determined from a medical history of surfactant administration, as such therapy was usually given to premature neonates with respiratory distress who required respiratory support of either continuous positive airway pressure (CPAP) or mechanical ventilation and supported by no radiological evidence of other diseases.[13] Transient tachypnea of newborn (TTN) was determined by the presence of respiratory distress that occurs immediately after birth and confirmed by a chest X-ray examination.

Patent ductus arteriosus (PDA) was routinely identified by echocardiography screening in premature neonates with <32 weeks' gestation on the first to fourth day of life. Ultrasonography of the head was performed to evaluate for intraventricular hemorrhage (IVH), and routinely carried out in the first week of life. If there was a clinical indication, ultrasonography of the head will be performed every week, but if the result was normal the next examination would typically be performed at 40 weeks of correction age. The IVH staging refered to the classification by Papile et al. which was later adapted using ultrasound as the equipment that portable.[14,15] The diagnosis of necrotizing enterocolitis (NEC) was classified according to Bell's criteria.[16] The diagnosis of retinopathy of prematurity (ROP) was established by ophthalmological examination in the fourth week of life. Fundoscopic findings were consistent with the international classification for ROP.[17]

Data were processed and analyzed using *Statistical Product and Service Solution (SPSS) for Windows version 16.0* software. Data are presented as median (range), mean (standard deviation), and percentage. The length of stay variable had a wide standard deviation and non-normal data distribution, so statistical analysis results used the median and range. This study was approved by the Bunda Hospital Medical Ethics Committee.

Results

Overall, 1,430 neonates were born at Bunda Women's and Children's Hospital, Jakarta in year 2021, of whom 366 (25.5%) neonates were from ARTs. From those there were 363 (25.3%) who underwent IVF program and 3 (0.2%) from insemination. Two neonates from the IVF program who were referred to other hospitals with indications of omphalocele and extreme prematurity with IVH were excluded, so 361 neonates from 186 pregnancies were included in this study. Most mothers who underwent IVF were ≤35 years (70.9%) of age, with mean aged of 33 years and in the first pregnancy (250; 69.2%). Most deliveries were performed by C-section (98.6%), although some mothers with an initial plan of normal labor failed induction. One hundred forty (38.7%) infants were delivered at preterm gestation (<37 weeks). Maternal complications noted were premature contractions

(16.6%), premature rupture of membranes (8.3%), and multiple pregnancies (twins) (31.5%) (**Table 1**).

Of 361 IVF-conceived neonates, most of them were born full term (221; 61.2%), while the 140 (38.7%) preterm deliveries occurred at a mean gestational age of 34.4 (SD 2.4) weeks, with most in the moderate to late preterm (32-36 weeks) category, and a small proportion born at post-term gestational age (1.6%). Subjects' mean birth weight was 2,800.2 (SD 640.3) grams, with 26.3% in the low-birth-weight category. The lowest birth weight was 670 grams in one neonate born at 25-week gestational age, following maternal complications in the form of contractions and antepartum bleeding (complete placenta previa). According to the Lubchenco chart10 to determine birth weight according to gestational age, 93.0% of subjects were in the appropriate-for-gestational age (AGA) category. Most neonates had good Apgar scores (7-10) in the first (92.2%) and fifth (99.7%) minutes (**Table 2**).

Of 273 neonates treated in the NICU during the study period, 88 neonates (32.2%) were conceived in IVF programs. Neonatal respiratory distress in the form of RDS was found in 40.9% of neonates and TTN was noted in 35.2% of neonates. Other morbidities of IVF neonates treated in NICU care included 11.3% with PDA based on echocardiography, 5.6% IVH, 15.9% NEC, 1.1 % ROP, and 9.0% neonatal sepsis (**Table 3**). The longest length of stay in the NICU was 100 days; one infant died within the initial 7 days of treatment. The overall mortality rate was 7.9% of NICU-treated neonates.

Table 1. Characteristics of mothers and newborn subjects

Characteristics	(N=361)
Maternal age, n (%)	
≤35 years	256 (70.9)
>35 years	105 (29.0)
Median (range), years	33 (19-48)
Mean (SD), years	33.2 (4.0)
Gravidity, n(%)	
1	250 (69.2)
≥2	111 (30.7)
Median (range)	1 (1-7)
Gestasional age n (%)	
<37 weeks	140 (38.7)
≥37 weeks	221 (61.2)
Median (range), weeks	37 (25-40)
Mean (SD), weeks	36.5 (2.3)
Maternal morbidity background, n (%)	
Premature rupture of membrane	30 (8.3)
Premature contractions	60 (16.6)
Antepartum bleeding	11 (3.0)
Gestational hypertension	22 (6.0)
Multiple gestations, n (%)	
Twin	114 (31.5)
Triplet	11 (3.0)
Method of delivery, n (%)	
Vaginal	5 (1.3)
C-section	356 (98.6)

Discussion

Most mothers who underwent the IVF program in our study were in the ≤35 years age group (70.9%), similar to other reports.[18,19] The relatively young maternal age may reflect early diagnosis and management of infertility. A study with cases population of women who visited fertility clinic found the most at the age of <35 years (71.4%), while less at the age ≥35 years (28.6%).[20] The latest data from *Riset Kesehatan Dasar/ RISKESDAS* (Indonesia Basic Health Research)

Table 2. Clinical profiles of neonates

Variables	(N=361)
Sex, n (%)	
Male	175 (48.4)
Female	186 (51.5)
Prematurity, n (%)	
Moderate to late preterm	120 (33.2)
Very preterm	14 (3.8)
Extremely preterm	6 (1.6)
Median (range), weeks	35 (25-36)
Mean (SD), weeks	34.4 (2.4)
Birth weight, n (%)	
Normal	253 (70.1)
LBW	95 (26.3)
VLBW	9 (2.5)
ELBW	4 (1.1)
Median (range), g	2,860 (670-4300)
Mean (SD), g	2,800.2 (640.3)
Weight for gestation, n (%)	
SGA	12 (3.3)
AGA	336 (93.0)
LGA	13 (3.6
Median Apgar score (range)	
1st minute	9 (3-9)
5th minute	10 (6-10)
Need for intensive care (NICU)	88 (24.3)

LBW=low birth weight; VLBW=very low birth weight; ELBW=extremely low birth weight; SGA=small for gestational age; AGA=appropriate for gestational age; LGA=large for gestational age

Table 3. Morbidities and mortality of IVF-conceived neonates in NICU

Variables	(N =88)
RDS, n (%)	36 (40.9)
TTN, n (%)	31 (35.2)
PDA, n (%)	10 (11.3)
IVH, n (%)	
Grade 1	2 (2.2)
Grade 2	3 (3.4)
Grade 3	
Grade 4	
NEC, n (%)	
Grade 1	12 (13.6)
Grade 2	2 (2.2)
Grade 3	-
ROP, n (%)	
Grade 1	-
Grade 2	1 (1.1)
Grade 3	-
Sepsis, n (%)	
Early	4 (4.5)
Late	4 (4.5)
Mortality	7 (7.9)

report in 2010 showed primary infertility in 5-5.9% of married women aged over 40 years and a higher rate (21.9%) in those aged 20-39 years.[21] Also in agreement with our findings, 69.2% of neonates came from mothers with a first pregnancy or who had never had a previous pregnancy (primary infertility).

In the early phase of ART implementation, the focus was on successful conception, but more recently the focus has shifted to achieve normal and healthy neonatal outcomes. Following the increase in IVF programs, several studies reported risks for both mother and baby.[7,22] From the *US National Reports* in 2015, the percentage of multiple pregnancy births in ART is higher (35.3%) than the total infant birth population (3.4%). At least 34% of neonates from ART were twins and 3% were triplets.5 In our study, of all IVF-conceived pregnancies, 31.5% were twin and 3% were triplet births. A study reported that the percentage of multiple births was 22.2% in IVF-conceived pregnancies. In a comparison of natural conception and IVF, multiple pregnancies were higher in IVF.[4] Another study found that mothers who underwent ART conception had a 54 times higher chance of multiple pregnancies.[22]

In order to reduce the incidence of multiple pregnancies while improving perinatal outcomes, many studies have focused on reduction of the number of embryos transferred into the uterus at one time. A study at *Morula IVF Clinic* at Jakarta that compared blastocyst elective single embryo transfer (eSET) to double embryo transfer (DET) significantly noted fewer low birth weight (95%CI 0.10 to 0.45; P<0.001) and preterm delivery (95%CI 0.13 to 0.49; P<0.001) in the eSET group than in the DET group. Though eSET efficiently reduced the need for NICU care and multiple pregnancies, there were no significant differences in perinatal mortality rates, Apgar scores, or maternal complications (gestational diabetes and hypertension in pregnancy).[23]

Increased multiple pregnancies in IVF were associated with preterm delivery and low birth weight.[5,22] In our study, the majority of neonates were born at 37 weeks gestation (61.2%), with an average of 36.5 (SD 2.3) weeks. However, 38.7% of our subjects were born preterm at an average of 34.4 (SD 2.4) weeks. In contrast, a previous study reported a higher percentage of preterm births (58.5%), with 45.6% of neonates having low birth weight.[22] A meta-analysis of 22 studies with a sample of 27,819 IVF-conceived neonates showed that more neonates were born prematurely than those conceived without ART (RR 1.54; 95%CI 1.47 to 1.62).[24] Similar findings were found in a retrospective cohort study that compared the obstetric and perinatal outcomes of 1,260 women on IVF, 1,899 subfertile women, and 2,480 fertile women; the OR for preterm delivery in IVF was 2.19 (95%CI 1.49 to 2.75).25 In line with our study, other studies reported a lower incidence of preterm birth, with a smaller percentage of low birth weight neonates.[3,18]

A case-control study at an army hospital in New Delhi also compared the outcomes of neonates born from ART and natural conceptions. They noted a >42 times higher risk of preterm delivery in women who had undergone ART conception (OR 41.9; 95%CI 15.5 to 113.1) and 22 times higher risk of delivering a low-birth-weight neonate (OR 22.3; 95%CI 8.8 to 56.5). However, when adjusted for preterm birth and multiple pregnancies, the risk of low birth weight became non-significant. Also, there may have been bias in that study because the case and control groups were not taken from the same hospital.[22] A study at the same hospital in the previous years reported 47.4% preterm births and 48.1% low birth weight.[18]

The most common maternal morbidity in our study was premature contractions (16.6%). Gestational diabetes and preeclampsia were the most common maternal outcomes in women who underwent IVF programs.[8] The trend of C-section deliveries was reported to be in line with increased IVF programs in Europe and the United States.[26] Most neonates in our study underwent C-section delivery (98.6%). A prospective study also reported the same finding: vaginal delivery was significantly lower and C-section was higher in the IVF group ($P<0.002$).[3] The most important factors that influenced the high rate of C-section delivery in that study were maternal age and IVF or precious pregnancy, which can describe high anxiety related to pregnancy management.[3] In our study, no observations were made in indications for either mode of delivery, so we could not analyze the causes of the high rate of cesarean delivery.

One of the neonatal outcome assessments was the Apgar score. In our study, the majority scored in the good category (7-10) for the first (92.2%) and fifth minutes (99.7%). Similar outcomes were reported in a 10-year retrospective study in Poland, where the most of neonates were in good condition and there was no difference between IVF and non-IVF groups in first-minute Apgar scores. However, for comparison, in their IVF group, significantly fewer neonates were in good condition based on the Apgar score at the fifth minute compared to non-IVF newborns (score 8-10: 325/334 *vs*. 304/305, respectively; $P=0.023$).27 Another retrospective study also found that 90.24% of neonates showed an Apgar score ≥7 at 5 minutes after birth.28 The Apgar score at the fifth minute after birth and the change between the first and fifth minutes are useful references for assessing resuscitation response. If at the age of the fifth minute, the Apgar score can reach or more than seven, then peripartum hypoxia or ischemia is less likely to cause neonatal encephalopathy.[29]

Observational studies of the effect of IVF on neonatal morbidity and mortality have begun to increase in recent years. In our study of 361 IVF neonates, 88 (24.3%) required NICU care. The highest neonatal morbidities from IVF pregnancies were RDS (40.9%) and TTN (35.2%). These morbidities may have been related to the fact that most neonates admitted to our NICU were preterm, so their respiratory physiology and other organ function were not well developed.[29] A previous study also reported that 25.4% of infants from IVF programs needed NICU care, with 40.6% (128/315) of infants coming from IVF pregnancy programs.[18] Also, a study from India reported that 75.6% of infants born to IVF-conceived pregnancies required treatment in NICU, with indications of prematurity and low birth weight.[28]

A study observed preterm neonates in the NICU and compared IVF and non-IVF groups revealed that gestational age and birth weight were significantly lower in IVF group, while multiple births, cesarean section, and antenatal steroid administration were significantly higher.[7] However, the IVF group showed increased preterm delivery, but not preterm mortality, whereas preterm morbidity other than IVH did not differ in the two groups. Gestational age was found to be the sole risk factor for IVH in this study.[7] Reports from previous studies also found no difference in morbidity or mortality between IVF and non-IVF neonates.[2,9]

The length of stay of infants from IVF-conceived pregnancies in our study varied so much that the data were not normally distributed. However, the longest length of stay was 100 days in one neonate with extreme prematurity; this child was mechanically ventilated. Similarly, a study reported that the longest length of stay in preterm IVF infants was 97 days.[7] Neonatal mortality of IVF infants in our study was 7.9% of NICU-treated subjects, while other studies reported 6.2%7 and 17.8%.[28] A limitation of our study was not comparing infants from natural and IVF conceptions during the same observation period, so we could not analyze whether infants from IVF had worse outcomes than non-IVF infants. In addition, other maternal factors such as infertility, socioeconomic status, and education were not analyzed. However, there have been very few studies in Indonesia that have investigated IVF-conceived neonate outcomes, so this descriptive data can be used as a reference for conducting furtherstudy. We recommend involving several centers to obtain a larger study population.

In conclusion, most mothers who underwent IVF programs are at a fairly young age, which could lead to an earlier diagnosis and management of infertility. Most IVF-conceived neonates are born at full term gestational age and normal birth weight, although the rate of preterm birth, low birth weight, need for NICU care, and mortality rate are quite high. Further

study is needed to assess the long-term outcomes of IVF neonates.

Conflict of interest

None declared.

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