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# Pediatric Biliary Atresia: Prenatal and Postnatal Risk Factors

Dina Aristiya Sumarno<sup>1</sup>, Sjamsul Arief<sup>2</sup>, Bagus Setyoboedi<sup>3</sup>

<sup>1</sup>Resident in Department of Child Health, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Hospital, Surabaya, Indonesia, <sup>2</sup>Lecturer and Consultant in Paediatric Hepatology Division Department of Child Health, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Hospital, Surabaya, Indonesia, <sup>3</sup>Lecturer and Consultant in Paediatric Hepatology Division Department of Child Health, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Hospital, Surabaya, Indonesia

## Abstract

**Background:** Biliary atresia is the most common cause of cholestasis in infants caused by intrauterine and neonatal inflammatory process leads to progressive biliary tract obstruction and fibrosis. Risk factors are expected to contribute in the disease type. Many studies have been done to determine the risk factors of biliary atresia. Yet, there is still limited information about risk factors in Indonesia. This study aims to determine the risk factors contributing to biliary atresia in East Java, Indonesia.

**Methods:** This cross-sectional study collected 219 medical record data of cholestasis patients during January 2010 to April 2017 that met the inclusion criteria. 85 of them were diagnosed with biliary atresia. Selected prenatal and postnatal risk factor were evaluated and analyzed.

**Result:** There were significant results in maternal age on pregnancy ( $p= 0.009$ ), parity ( $p= 0.035$ ), and gestational age ( $p= 0.005$ ) among 85 patients which were diagnosed with biliary atresia. The regression test showed significant result on those 3 factors.

**Conclusion:** Maternal age on pregnancy, parity, and gestational age are the prenatal and postnatal risk factors that contribute to the biliary atresia incidence. These results are expected to be used as one of the providing information regarding prenatal and postnatal risk factors for pediatric biliary atresia in East Java, Indonesia

**Keyword** *Biliary Atresia, Risk Factor, Prenatal, Postnatal*

## Background

Biliary atresia is well known as a progressive obstructive cholangiopathy affecting biliary tract, both in the intrahepatic and extrahepatic tract, resulting in cirrhosis, liver failure, and death if it is not well treated. It also becomes the most common cause

of pediatric cholestasis besides infection and  $\alpha$ -1 antitrypsin deficiency<sup>1</sup>. Despite the poor prognosis and complications in delayed diagnosis, the clear etiology and pathophysiology are remained unknown. The incidences of biliary atresia are reported around the world. Biliary atresia seems to be more commonly occurred in Asia than Europe or America, with the incidence approximately 1:8000 in Asia compared to 1: 15,000-20,000 in Europe or America<sup>2,3</sup>. Another study also stated that Asia-pacific region (1:3300) has higher biliary atresia incidence than Europe (1:18000)<sup>4</sup>.

The initial findings of this disease are quite similar to other condition like physiological neonatal icteric, thus the diagnosis is likely to be delayed and the

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### Corresponding author:

**Bagus Setyoboedi, MD**

Lecturer and Consultant in Paediatric Hepatology Division Department of Child Health, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Hospital, Surabaya, Indonesia



prognosis becomes worse. There are two major forms of biliary atresia, embryonic form, which is related to other congenital disorders, and perinatal form, where normal bile duct underwent fibro-obliteration during perinatal period<sup>3</sup>. Some risk factors, including environment, prenatal, and postnatal risk factors, play significant role to determine the type and form of biliary atresia.

Many researches around the world have been done to describe the risk factors of biliary atresia incidences. Previous study reported that genetical factor or chromosome alteration, viral-induced immune dysregulation, maternal disease including gestational diabetes, are several factors that affect the incidence of biliary atresia<sup>3</sup>. Another older study suggests that maternal age, parity and gravidity, gestational age, Intrauterine Growth Retardation (IUGR), birth weight, and race/ethnic as the potential risk factors for pediatric biliary atresia<sup>5</sup>. The clear However, in Indonesia, data showing the biliary atresia risk factors is still limited. The authors aim to describe both the prenatal and postnatal risk factors in children with biliary atresia.

### Methods and Materials

This was a cross-sectional study conducted in April 2017 using medical record data of children aged a-month-old to 72-months-old that were diagnosed with cholestasis in pediatric hepatology outpatient ward in Dr. Soetomo Hospital Surabaya during January 2010 to April 2017. Any incomplete data in medical record were excluded.

The diagnosis of biliary atresia was decided based on clinical manifestation (icteric, acholic stool), laboratory finding (direct bilirubin > 2 mg/dL if total bilirubin < 5 mg/dL, or 20% of total bilirubin if its value > 5 mg/dL), and histological findings of liver biopsy (ductular proliferation, periportal fibrosis, and bile plug).

We evaluated the maternal age on pregnancy, maternal history on pregnancy, and maternal parity as the prenatal risk factors and Birth weight, gestational age, gender, plurality, anti CMV serology as postnatal risk factors. The data were collected and analyzed by chi square and prevalence ratio was evaluated for subsequently. All statistical analysis was conducted using SPSS version 25.

### Result

There were total 219 patients with cholestasis that met the inclusion criteria. Among those patients, 85 patients (38.8%) were diagnosed with biliary atresia and 134 (61.2 %) were not biliary atresia. The characteristics of the subjects were depicted in table 1.

**Table 1. Data Characteristic Including Prenatal and Postnatal Risk Factors of Biliary Atresia**

Characteristic Profile	Biliary Atresia (n=85)	Non-Biliary Atresia (n=134)
Age		
0-6 m.o	51 (41.5 %)	72 (58.5 %)
6 m.o – 12 m.o	28 (35.0 %)	52 (65.0 %)
12 m.o – 36 m.o	5 (50 %)	5 (50.0 %)
36 m.o – 72 m.o	1 (16.7 %)	5 (83.3 %)
Gender		
Girl	49 (44.5 %)	61 (55.5 %)
Boy	36 (33.0 %)	73 (67.0 %)
Domicile		
Surabaya	34 (38.2 %)	55 (61.8 %)
Outside Surabaya	51 (39.2 %)	79 (60.8 %)



**Cont... Table 1. Data Characteristic Including Prenatal and Postnatal Risk Factors of Biliary Atresia**

Maternal Age on Pregnancy < 35 y.o. ≥ 35 y.o.	38 (31.1 %) 47 (48.5 %)	84 (68.9 %) 50 (51.5 %)
Maternal history on pregnancy Hypertension Diabetes Mellitus Healthy	19 (48.7 %) 14 (43.8 %) 52 (35.1 %)	20 (51.3 %) 18 (56.3 %) 96 (64.9 %)
Maternal Parity < 5 times ≥ 5 times	41 (32.5 %) 44 (47.3 %)	85 (67.5 %) 49 (52.7 %)
Birth Weight < 2500 g ≥ 2500 g	35 (39.8 %) 50 (38.2 %)	53 (60.2 %) 81 (61.8 %)
Gestational Age Premature Aterm	51 (48.6 %) 34 (29.8 %)	54 (51.4 %) 80 (70.2 %)
Plurality Single Multiple	81 (38.2 %) 4 (57.1 %)	131 (61.8 %) 3 (42.9 %)
Ig G and Ig M anti-CMV IGM + IgG + Ig G and Ig M +	11 (28.2 %) 42 (37.5 %) 32 (47.1 %)	28 (71.8 %) 70 (62.5 %) 36 (52.9 %)

In Table 2, the Chi square bivariate analysis showed that maternal age on pregnancy ( $p= 0.009$ ,  $PR= 2.07$ ) and parity (0.035) differed significantly, in contrast with the maternal history on pregnancy ( $p= 0.247$ ,  $PR= 1.86$ ). Furthermore, Table 3 presented the analysis result on postnatal risk factors, where gestational age ( $p= 0.005$ ,  $PR= 1.27-3.86$ ) was the only risk factor in postnatal that differed significantly.

**Table 2. Prenatal Risk Factors in Pediatric Biliary Atresia**

Variable	n (%)	Prevalence Ratio (PR)	CI 95%	P
Maternal age on pregnancy < 35 y.o. ≥ 35 y.o.	38 (44.7) 47 (55.3)	2.07	1.19-3.61	0.009
Maternal history on pregnancy Hypertension Diabetes Mellitus Healthy	19 (22.4) 14 (16.5) 52 (61.2)	-	-	-
Maternal parity < 5 times ≥ 5 times	41 (48.2) 44 (51.8)	1.86	1.07-3.23	0.035

**Table 3. Postnatal Risk Factors in Pediatric Biliary Atresia**

Variable	N (%)	PR	CI 95 %	P
Gender Girl Boy	49 (57.6) 36 (42.4)	-	-	0.096
Birth Weight < 2500 g ≥ 2500 g	35 (41.2) 50 (58.8)	-	-	0.888
Gestational Age Premature Aterm	51 (60.0) 34 (40.0)	2.22	1.27-3.86	0.005
IgG and IgM anti CMV IgM + IgG + IgG and IgM +	11 (12.9) 42 (49.4) 32 (47.1)	-	-	0.144
Plurality Single Multiple	81 (95.3) 4 (4.7)	-	-	0.435

The logistic regression analysis showed that maternal age on pregnancy ( $p= 0.002$ ), parity ( $p= 0.015$ ), and gestational age ( $p= 0.002$ ) are 3 most influential factors on the biliary atresia incidence. The data is depicted in table 4.

**Table 4. Multivariate Analysis on Prenatal and Postnatal Risk Factors in Pediatric Biliary Atresia**

Risk Factors	Exp(B)	CI 95%	P
Maternal age on pregnancy	0.383	0.21 – 0.69	0.002
Parity	0.482	0.26 – 0.86	0.015
Gestational Age	0.386	0.21 – 0.70	0.002
Gender	0.594	0.33 – 1.06	0.081
Constant	1.972		

### Discussion

Among 219 patients, 85 patients were diagnosed with biliary atresia. The diagnosis is based on clinical manifestation, laboratory finding, and histological finding after liver biopsy. Liver biopsy procedure has been known as a predictor and differentiator between biliary atresia and non-biliary atresia in cholestasis

patient<sup>6,7</sup>. There are more non-biliary atresia patients than biliary atresia in this study. Some other studies stated differently that biliary atresia is the most cause of cholestasis in children<sup>5,8</sup>.

The advanced maternal age ( $\geq 35$  y.o) on pregnancy is associated with unfavorable outcome of delivery (premature, low birth weight, other complications)<sup>9</sup>. A

study done in Sweden showed the similar result with this study where a mother whose age  $\geq 35$  years old has higher risk to have a children with biliary atresia<sup>5</sup>. Old maternal age on pregnancy is a fetomaternal factor that contribute to biliary atresia incidence. Older mother is associated with oocyte aging, history of prior disease, and chromosome abnormalities toward the baby<sup>10,11</sup>.

Maternal history on pregnancy, including asthma, diabetes mellitus, epilepsy, urinary tract infection, respiratory infection, gastrointestinal infection, and healthy. A study stated that there is no significant association between maternal history on pregnancy with the biliary atresia incidence<sup>12</sup>. Another study stated that diabetes mellitus and hypertension are included to risk factors of biliary atresia incidence. In diabetes mellitus mother, vascular dysfunction stimulate the hypoxia-induced ischemia in fetal liver vascularization<sup>13</sup>. Furthermore, gestational hypertension can cause several complications and poor outcome, including premature delivery, intrauterine growth retardation (IUGR), and death. High blood pressure decreases the placental blood flow and creates circulation disruption and nutrition transfer delay that lead to premature delivery. Direct association between gestational hypertension and biliary atresia incidence has not been established, but it may affect the biliary atresia incidence through the premature delivery incidence<sup>3</sup>.

High parity rate is defined as maternal delivery event more than 5 times with gestational age in each pregnancy is more than 20 weeks<sup>14</sup>. The parity data finding in this study has similar result in other studies<sup>5,14</sup>. A study assumed that higher parity leads to a potential risk factor of having fetal growth abnormalities, including low birth weight and premature delivery, but the mechanism is still unknown<sup>14</sup>.

Birth weight is classified into two groups, low birth weight (< 2500 gram) and normal birth weight ( $\geq 2500$  gram). a low birth weight is associated with sequences of public health problem consequences<sup>15</sup>. Previous study showed that there is no significant association between low birth weight and biliary atresia incidence, but premature delivery has significant association with this disease<sup>5</sup>. Prematurity has been reported as a risk factor for biliary atresia incidence despite of unclear mechanism. Some previous studies have reported the

significant association between biliary atresia and prematurity<sup>16-18</sup>.

Gender has been suggested as one of the risk factors of biliary atresia. Many studies have been evaluating how gender differences affect the biliary atresia incidence with the different results. An epidemiological study in Korea discovered that female infant has higher risk in biliary atresia incidence than male infant<sup>19</sup>. Other studies also showed similar result<sup>20,21</sup>. On the other hand, a study in Sweden stated differently that higher biliary atresia prevalence found in male infants than female<sup>5</sup>.

Plurality defined as the number of the children born in a delivery. A study in Texas reported a biliary atresia incidence in monozygotic/identical twins. A recent meta-analysis study of 12 articles stated that biliary atresia is found in almost half of twin subjects with monozygotic and dizygotic twins share the same proportion<sup>22</sup>.

## Conclusion

Among several prenatal factors that have been established, the presence of maternal age  $\geq 35$  years old on pregnancy and maternal parity ( $\geq 5$  times) are two times higher to develop a biliary atresia. Whereas in postnatal factor, presence of prematurity risks twice higher to develop a biliary atresia. This study result may be a providing information to determine the risk factors of biliary atresia in Indonesia. **Conflict of interest** : None declared.

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