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Incidence, Ultrasonographic Findings, and Pregnancy Outcomes in Cases of Hydrops Fetalis at Thammasat University Hospital

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ABSTRACT

OBJECTIVE: To investigate the incidence, ultrasonographic findings, and pregnancy outcomes of hydrops fetalis at Thammasat University Hospital. MATERIALS AND METHODS: A retrospective study was conducted. Inclusion criteria required that all participants had gestational age (GA) confirmed by ultrasound for pregnancies of less than 20 weeks. RESULTS: In total, 171 pregnant women participated in this study, and 10 cases were excluded due to incomplete data. This study was conducted on 161 pregnant women for analysis. The mean GA at diagnosis was 23.4 ± 4.9 weeks. The most crucial etiology of hydrops fetalis was Hb Bart's disease (41.6%). Other etiologies included chromosomal abnormalities (11.2%), structural abnormalities (5%), infections (3.1%), and hemoglobinopathies (non-Hb Bart's disease) (2.5%). The percentage of etiologies that could not be identified was 36.6%. Most cases of Hb Bart's disease were found after a GA of 20 weeks, as indicated by the ultrasound findings, and included conditions such as ascites and cardiomegaly. Further, 44.4% of the group with chromosomal abnormalities were found earlier than 20 weeks and had ascites and skin edema; trisomy 21 was the primary cause. Fifty percent of the structural abnormalities group were found before 20 weeks. Most infectious groups presented late compared to the others, and syphilis was the primary cause. CONCLUSIONS: The most common cause of hydrops fetalis was Hb Bart's disease, followed by chromosomal abnormalities, structural abnormalities, and then infections. Ascites was the most common finding in all etiologies. However, in the group of ongoing pregnancies with negative investigations, there were good outcomes with viable newborns.

Keywords: Bart's hydrops fetalis; Hydrops fetalis; Thalassemia; Ultrasonographic findings

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1. Introduction

Hydrops fetalis is a severe obstetric condition that can have very complicated consequences, such as maternal preeclampsia (PIH), mirror syndrome, postpartum hemorrhaging, abnormal coagulopathies, and maternal death [1-3]. Several causes of hydrops fetalis can be found, such as Hb Bart's disease, chromosomal abnormalities, structural abnormalities, infection, Rh incompatibilities, and other unknown causes [4-7]. In addition, etiology may differ by region due to racial makeup of the local population. For example, structural abnormalities are the primary cause of hydrops fetalis in Europe, whereas Hb Bart's disease is the main cause in Asia. [4-9, 18]. Treatment of these conditions depends on their causes and includes measures such as abortion, continuation of pregnancy, and intrauterine treatment.

Due to the limited amount of information, incomplete data, and small sample size in Thailand, the causes of hydrops fetalis and long-term pregnancy-related outcomes were also limited [5, 6,16, 17]. Therefore, we were interested in verifying the incidences of this condition by studying the ultrasonographic findings and pregnancy outcomes of hydrops fetalis in the Thai population. In this way, we searched for new knowledge and made plans to practice appropriate management in our clinical practice.

2. Materials and Methods

The research protocol was reviewed and approved by the Ethics Committee of Thammasat University Hospital (registration number MTU-EC-OB-0-073/63). The retrospective study was conducted between October 2020 and October 2021 at Thammasat University Hospital. Pregnant women with hydrops fetalis who presented to the antenatal outpatient clinic or maternal-fetal medicine (MFM) department at Thammasat University Hospital were eligible to participate. Inclusion criteria required that all participants had a gestational age (GA) of less than 20 weeks, confirmed by ultrasound. In addition, the exclusion criteria were multiple pregnancies and incomplete records.

A study by Suwanrath-Kengpol et al. [5] found that the incidence of hydrops fetalis with a known cause was 87.3%, while the number of participants in their study was 153. With an attrition rate of 10% of participants, the total sample size was scaled up to 171 pregnant women.

Data collected included demographic data, GA at the time of hydrops fetalis diagnosis, ultrasonographic findings, laboratory tests, causes, and pregnancy outcomes.

Primary outcomes were the incidence and ultrasonographic findings of hydrops fetalis. Secondary outcomes were the causes of hydrops fetalis and pregnancy outcomes. Hydrops fetalis was defined as abnormal amounts of fluid in two or more fetal compartments, including ascites, pleural effusion, and pericardial effusion, or in one compartment associated with generalized cutaneous edema. The definition of cardiomegaly was a cardiothoracic (C/T) circumference greater than 0.5. The definition of fetal anemia was a Doppler evaluation of fetal middle cerebral artery peak systolic velocity (MCA-PSV) $\geq$ 1.5-fold the median (MOM). The definition of normal amniotic fluid (AF) was the deepest vertical pocket (DVP) 2-8 cm or an amniotic fluid index (AFI) of 5-25 cm. The definition of placentomegaly was having a placental thickness > 4 cm. Adverse maternal outcomes were defined as PIH, postpartum hemorrhage (PPH), disseminated intravascular coagulation (DIC), and maternal death. Adverse neonatal outcomes were a dead fetus in utero (DFIU), stillbirth, neonatal intensive care unit (NICU) admission within 48 hours of delivery, neonatal sepsis, an Apgar score of less than 7 at 5 minutes, respiratory distress syndrome

(RDS), transient tachypnea of the newborn (TTNB), and anemia

Statistical analysis was performed using SPSS version 22 (SPSS Inc, Chicago, IL, USA). Continuous data are presented as mean ± standard deviation (SD); categorical data are presented as n (%).

3. Results

One hundred seventy-one pregnant women were enrolled in this study. However, only 161 of the pregnant women had their data completed for analysis. Ten cases were excluded due to incomplete records. Maternal characteristics are shown in Table 1. The mean GA at diagnosis was 23.4 ± 4.9 weeks. Seventy-seven percent of cases were detected after the 20th week of gestation.

Table 1. Demographic characteristics of pregnant women with hydrops fetalis.

Maternal characteristics	Total number = 161
Maternal age (years)	30.6 ± 5.5
GA at first ANC (weeks)	11.1 ± 0.36
Number of total ANC	7.1 ± 2.8
BMI at pre-pregnancy (kg/m^2)	22.9 ± 2.5
Place of ANC	
- Thammasat University Hospital	43 (26.7)
- Others	118 (73.3)
GA at detection (weeks)	23.4 ± 4.9
- ≤ 20	37 (23)
- > 20	124 (77)

GA: gestational age, ANC: antenatal care, BMI: Body mass index
Data are presented as n (%), or mean ± SD

Hb Bart's disease was the most common cause of hydrops fetalis (41.6%). Other causes were chromosomal abnormalities (11.2%), structural abnormalities (5%), infections (3.1%), and hemoglobinopathies (non-Hb Bart's disease, 2.5%). Despite investigations of the possible causes, the etiology remained unclear in about one-third (36.6%) of cases (Fig.1). Different causes were associated with different GAs, as shown in Table 2.

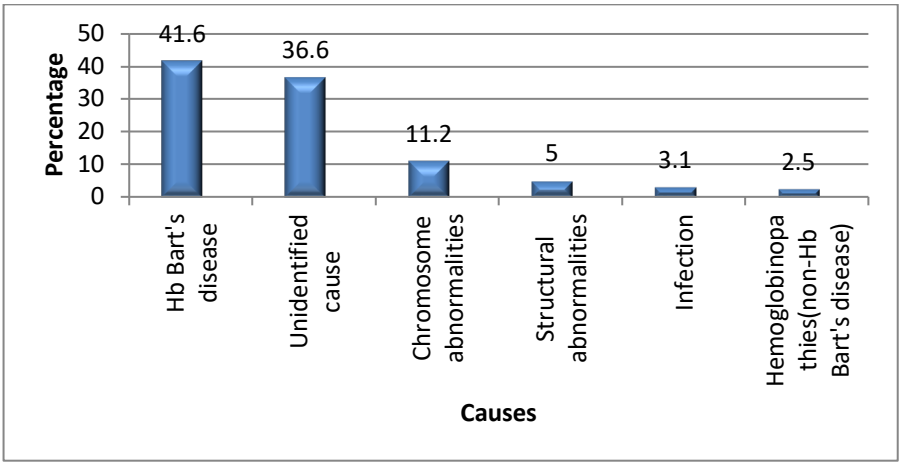

Fig. 1. Causes of hydrops fetalis at Thammasat University Hospital (%).

Table 2. Causes of hydrops fetalis by GA.

Cause (n)	GA (weeks) 12-20	20^{+1}-26	26^{+1}-34
Hb Bart's disease (67)	10 (15)	34 (50.7)	23 (34.3)
Chromosome abnormalities (18)	14 (77.8)	4 (22.2)	-
Structural abnormalities (8)	5 (62.5)	1 (12.5)	2 (25)
Infection (5)	-	1 (20)	4 (80)
Hemoglobinopathies (non-Hb Bart's disease) (4)	-	3 (75)	1 (25)
Unidentified cause (59)	8 (13.6)	34 (57.6)	17 (28.8)

GA: gestational age, Data are presented as n (%).

3.1 Hb Bart's Disease

Of the 67 cases of Hb Bart's hydrops fetalis, most were found after the 20th week of gestation, and none were detected in the first trimester (Table 2). The most common ultrasonographic findings were cardiomegaly and ascites, with a prevalence of 92.5% and 89.6%, respectively. The less common findings were pericardial effusion and fetal anemia. Abnormal amniotic fluid was found with a prevalence of 19.4%, and most cases were either oligohydramnios or anhydramnios (Table 3). All mothers were counseled and decided to terminate their pregnancy due to poor prognosis.

3.2 Chromosomal abnormalities

Of the 18 cases of chromosomal abnormalities, 14 (77.8%) occurred among participants before the 20th week of gestation (Table 2). The most common ultrasonographic findings were generalized skin edema and ascites. Neither fetal anemia nor abnormal amniotic fluid was detected in any of the cases (Table 3). Trisomy 21 was the primary cause of this outcome (66.7%). Others were Turner syndrome (27.8%) and trisomy 18 (5.5%). Almost all cases ended in abortion, and only 1 case (with trisomy 21) chose to continue the pregnancy, although this case resulted in neonatal death of the child after birth.

3.3 Structural abnormalities

Of the 8 cases of structural abnormalities studied, 5 (62.5%) were detected before the 20th week of gestation (Table 2). Structural abnormalities were micromelia (3 cases), Ebstein's anomaly (2 cases), arthrogryposis (1 case), congenital pulmonary airway malformation (CPAM) type 1 (1 case), and irregular premature atrial contraction (PAC) (1 case). The most common ultrasonographic findings were cardiomegaly and ascites. In addition, most of them had normal amniotic fluid, as shown by the ultrasonographic findings (75%) (Table 3), and 62.5% resulted in pregnancy termination due to poor prognosis. Only CPAM and PAC had a good pregnancy prognosis.

3.4 Infection

Of the 5 cases of infection studied, most (80%) were detected as hydrops fetalis after the 26th week of gestation (Table 2), 60% were syphilis infections, and others were cytomegalovirus (CMV) infections. The most common ultrasonographic findings were ascites (100%), pericardial effusion (80%), and cardiomegaly (80%), while fetal anemia was detected in 2 of the 5 cases (40%). No abnormal amniotic fluid was found (Table 3). Sixty percent of cases ended in abortions due to poor prognosis, and 20% were DFIU. None of the fetuses survived.

3.5 Hemoglobinopathies (Non-Hb Bart's disease)

Of the 4 cases of hemoglobinopathies (non-Hb Bart's disease) collected, all were found to have hydrops fetalis after the 20th week of gestation, according to Bart hydrops fetalis (Table 2). The most common ultrasonographic findings were cardiomegaly and ascites. Seventy-five

percent of these cases had an average amniotic fluid volume (Table 3). Hemoglobin (Hb) typing results by cordocentesis indicated EF Bart's with abnormal hemoglobin (3 cases). Two cases received counseling due to poor prognosis caused by severe fetal anemia and anhydramnios. Subsequently, abortion was performed in both cases. One case was a perinatal death, and the other was FA Bart's with abnormal hemoglobin. The result was a viable newborn who did not require a blood transfusion after birth.

3.6 Unidentified cause

Of the 59 cases where no underlying cause could be identified, 86.4% were diagnosed after the 20th week of gestation (Table 2), and 41 cases (69.5%) were not investigated because ultrasound findings revealed a poor prognosis, such as marked generalized skin edema and severe cardiomegaly. Financial problems arose in these cases. Of the 18 cases that underwent investigation, cordocentesis was performed in 17 cases and amniocentesis in 1 case to investigate the presence of a karyotype. Hb typing and TORCH (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus) titers could not be identified as the cause. These 8 received counseling about their poor prognosis, after which their pregnancies were terminated following investigation. The number of ongoing pregnancies included 10 cases. Five of the 10 cases (50%) resulted in a DFIU within 24 hours of intervention. One case was a DFIU at 35 weeks of gestation due to severe fetal growth restriction with reversed umbilical artery diastolic flow. One case ended in perinatal death at GA 33+1 weeks due to fetal distress from amniotic fluid leakage with a prolapsed umbilical cord. In 3 of the 5 cases (60%), serial ultrasonography revealed that the hydrops fetalis regressed and delivery was normal.

Iatrogenic DFIU within 24 hours of the procedure was noted in 8 cases (8.7%). Adverse maternal outcomes were PPH (1.2%) and PIH (0.6%). Adverse neonatal outcomes were DFIU (3.7%), neonatal death (3.7%), NICU admission within 48 hours (0.6%), and anemia (0.6%).

Table 3. The relationship between the causes of hydrops fetalis and ultrasonographic findings.

	ascites	pericardial effusion	pleural effusion	cardiomegaly	generalized skin edema	fetal anemia	abnormal AF	placentomegaly
Hb Bart's disease (67)	60 (89.6)	45(67.2)	24 (35.8)	62 (92.5)	21 (31.3)	40 (59.7)	13 (19.4)	29 (43.2)
Chromosome abnormalities (18)	16 (88.9)	-	-	1 (5.6)	17 (94.4)	-	-	-
Structural abnormalities (8)	6 (75)	5 (62.5)	5 (62.5)	7 (87.5)	5 (62.5)	1 (12.5)	2 (25)	1 (12.5)
Infection (5)	5 (100)	4 (80)	1 (20)	4 (80)	1 (20)	2 (40)	-	1 (20)
Hemoglobinopathies (non-Hb Bart's disease) (4)	4 (100)	3 (75)	1 (25)	4 (100)	-	2 (50)	1 (25)	-
Unidentified cause (59)*	50 (84.7)	29 (49.2)	19 (32.2)	35 (59.3)	43 (72.9)	22 (37.3)	22 (37.3)	22 (37.3)
Negative investigation (18)**	4 (22.2)	8 (44.4)	6 (33.3)	7 (38.9)	2 (11.1)	2 (11.1)	5 (27.8)	2 (11.1)

GA: gestational age, USG: ultrasonography, AF: amniotic fluid *Unidentified cause (no investigation and negative investigation, n=59), **Negative investigation (n=18), Data are presented as n (%).

Table 4. Summary of hydrops fetalis identified in different regions.

	This study	Suwanrath-Kengpol et al.[5]	Thawalwong et al.[6]	Taweevisit and Thorner[15]	He et al.[7]	Dahua et al.[16]
Number	161	71	82	78	482	1004
Region	Central Thailand	Southern Thailand	Northeast Thailand	Central Thailand	Southern China	Southern China
Incidence (/1,000 total births)	2.06	2.8	1.8	-	-	7.9
GA at diagnosis (weeks)	23.4 ± 4.9	26 (14-39)	25	28	24 (13-35)	23
Etiologies						
- Hb Bart's disease	67 (41.6)	20 (28.2)	30 (36.6)	17 (21.8)	298 (61.8)	267 (26.6)
- Chromosome abnormalities	18 (11.2)	7 (9.9)	2 (2.4)	-	65 (13.5)	199 (19.8)
-Trisomy 21	12	1	-	-	16	-
- Others	6	6	2	-	49	-
- Structural abnormalities	8 (5)	11 (15.5)	3 (3.7)	23 (29.5)	40 (8.3)	-
- Infection	5 (3.1)	9 (12.7)	3 (3.7)	5 (6.4)	7 (1.5)	26 (2.6)
- Non-Hb Bart's disease	4 (2.5)	-	-	3 (3.8)	-	18 (1.8)
- Others	-	24 (33.8)	5 (6.1)	21 (26.9)	9	125 (12.5)
- Unidentified cause*	59 (36.6)	9 (12.7)	39 (47.6)	9 (11.5)	63 (13.1)	282 (28.1)
- Negative investigation**	18 (15)	-	-	-	-	-
Pregnancy outcomes						
- TOP	143 (88.8)	47 (66.2)	-	-	459 (95.2)	672 (67)
- DFIU	7 (4.3)	12 (17)	40 (48.8)	78 (100)	14 (3)	26 (2.6)
- Neonatal death	5 (3.1)	7 (9.9)	41 (50)	-	6 (1.2)	16 (1.6)
- Live birth	6 (3.7)	3 (4.1)	1 (1.2)	-	3 (0.6)	198 (19.7)
- No data	-	2 (2.8)	-	-	-	92 (9.1)

GA: gestational age, CMV: cytomegalovirus, TOP: termination of pregnancy, DFIU: dead fetus in utero*Unidentified cause (n=59),**Negative investigation (n=18), Data are presented as n (%), mean ± S

4. Discussion

Data were compiled from a birth registry of medical records from 2006 to 2021 and showed a total of 78,152 births at Thammasat University Hospital. The number of cases of hydrops fetalis was 161, and the incidence rate was 2.06 per 1,000 total births, which is consistent with the findings of Suwanrath-Kengpol et al. [5] and Thawalwong et al. [6]. In addition, the average GA at diagnosis was 23 weeks, which is consistent with the results of a previous study.

In our study, we demonstrated that the major causes of hydrops fetalis were Hb Bart's disease (41.6%), chromosomal abnormalities (11.2%), structural abnormalities (5%), infections (3.1%), hemoglobinopathies (non-Hb Bart's disease) (2.5%), and unidentified causes (36.6%). These findings were similar to a report from China by He, et al. in 2017 [7]. Similarly, the most common causes of hydrops fetalis were also identified in a study by Suwanrath-Kengpol et al. [5], and Thawalwong et al. [6] in Thailand and Yang et al. [8] in Taiwan. However, these results differed in detail, indicating that the leading causes of hydrops fetalis were Hb Bart's disease, followed by structural abnormalities, infections, chromosomal abnormalities, and unidentified causes. One factor possibly associated with a lower number of structural abnormalities was the increased accuracy of ultrasonography. In addition, the data showed variation in etiology depending on the ethnic population and region studied, which differs from a report by Braun et al. done in various Western countries [9], and Santo et al. [10] which showed that structural abnormalities were the major cause of hydrops fetalis in Europe.

Most cases of Hb Bart's disease were found after the 20th week of gestation, which is consistent with He et al. [7], Liao et al. [11], Jatavan et al. [12], and Tongsong et al. [13]. Fetuses can survive the early phase of pregnancy because they still produce small amounts of Hb Portland I and II that do not result in hydrops fetalis. The most common ultrasound findings were cardiomegaly and ascites, followed by fetal anemia, which is similar to the findings of previous studies [11-13]. Unlike the study by Luewan et al. [17], fetal anemia here was found to be an early sign of hydrops fetalis, which can be explained by compensatory observations. This is not the same in every individual. This finding may be beneficial in conjunction with a serial USG examination in patients with Bart's hydrops fetalis.

Chromosomal abnormalities were the second most common cause of hydrops fetalis in our study, unlike in previous studies conducted in Thailand [5-6]. In 77.8% of the affected groups, hydrops fetalis was detected before 20 weeks of gestation, earlier than the onset of Hb Bart's disease, which agrees with findings by He et al. [7]. Trisomy 21 was the leading cause of chromosomal abnormalities; however, this finding was inconsistent with previous studies [5-6, 16], which found Turner syndrome to be the leading cause. This syndrome may have been described in populations used in our study of patients older than those in previous studies.

Structural abnormalities are mostly found as hydrops fetalis before 20 weeks of gestation, which is earlier than what was reported in previous studies [5-7]. This difference may be because routine ultrasound examinations were performed early in the MFM unit to confirm GA. The primary causes were cardiac defects and skeletal dysplasia.

Most of the infections were hydrops fetalis after 26 weeks of gestation, which is consistent with previous findings by He et al. [7] and Cubel et al. [14]. However, our study found that syphilis to be the most common cause of infection that led to hydrops fetalis, followed by CMV. These findings differ from He et al. [7], Cubel et al. [14], and Désilets et al. [4], who determined that parvovirus B19 was the primary cause. In a report by Taweevisit and Thorner [15], CMV was found to be the only infecting pathogen. Most participants had asymptomatic infections and had not been previously treated. Factors that could lead to an increase in syphilis infections in our study were low socioeconomic status and no annual screening, which explained the poor pregnancy outcomes in the infection group.

In the cases with hemoglobinopathies (non-Hb Bart's disease), the ultrasound findings and GAs at diagnosis of hydrops fetalis were the same as in Hb Bart's disease. All were Hb H with abnormal Hb, as in alpha-thalassemia. This finding differed from the report by Taweevisit and Thorner [15], stating that it was Hb H disease. It was found that 75% of cases had a poor prognosis because Hb A was not detected.

Of the group with unidentified causes, 41 cases (69.5%) were not investigated. Sonographic findings revealed more than two features, such as generalized skin edema, cardiomegaly, ascites, and fetal anemia. These findings may indicate a poor prognosis. Thus, negative examinations accounted for 15% of all cases (18 out of 120 cases), which is consistent with findings by Suwanrath-Kengpol et al. [5], Taweevisit and Thorner [15], and He et al. [7], who found that 60% of patients in the continued-pregnancy group had good neonatal outcomes. They were healthy and had no complications. In these groups, patients did not have generalized skin edema or fetal anemia, which could indicate good prognostic factors.

Our study detected most chromosomal and structural abnormalities at a GA of 12-20 weeks. Cases of Hb Bart's disease were observed at 20 weeks, and infections were detected at 26 weeks of gestation. Ascites were the most common finding in all etiologies, with a low incidence of adverse

maternal and neonatal outcomes, attributable to appropriate management and effectiveness of the multidisciplinary team in tertiary hospitals. No maternal deaths were reported in this study.

There were some limitations to our retrospective study. First, we were not able to collect and detect the information and fully perform the laboratory investigations, which prevented investigations in accordance with the rights of patients in Thailand, resulting in higher treatment costs. Second, was the occurrence of unexplained causes of hydrops fetalis, such as inborn errors of metabolism and genetic syndromes, because treatment of these conditions is limited to advanced technologies, unavailable to this study. A major benefit of this study is that it provides an update of our data in the form of an overview of hydrops fetalis and pregnancy outcomes in Thailand, which differs in several aspects from our previous study. Now currently, syphilis infections constitute a significant problem that we should be aware of because early treatment can change the prognosis to be more positive. In our group with negative examination results, there were still ultrasound findings that could indicate good outcomes, such as no generalized skin edema or fetal anemia. These findings can now be used to counsel pregnant women with negative examination results. However, a future study should be conducted prospectively to collect complete data and perform a comprehensive laboratory investigation.

5. Conclusion

The most common etiology was Hb Bart's disease, followed by chromosomal abnormalities, structural abnormalities, and then infections. The most common chromosome abnormality was trisomy 21. Syphilis was the main source of infection. The average GA of patients diagnosed with hydrops fetalis in the chromosomal and structural abnormalities group was earlier than both those with Hb Bart disease and those in the infection group. The type of treatment depended on the cause of hydrops fetalis. A low incidence of adverse maternal outcomes was noted. However, there were good results with viable newborns in the group of continued-pregnancies with negative examinations.

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