Non-immune hydrops fetalis in the first trimester: A review of 30 cases

H. Recep, *M.D.*

Department of Obstetrics and Gynecology, Faculty of Medicine, University of Istanbul (Turkey)

Summary

Objective: To evaluate the etiology and outcome of non-immune hydrops fetalis diagnosed in the first trimester of pregnancy.

Methods: 30 cases with fetal hydrops diagnosed between 10 and 14 weeks of pregnancy at the prenatal diagnosis unit of Istanbul Medical Faculty were reviewed. Sonographic findings, fetal chromosome profiles, and outcomes were analyzed.

Results: NIHF was found to be associated with structural abnormalities in 25 (83.3%) cases, and chromosomal abnormalities in nine (47.3%) of the 19 analyzed cases. Nuchal translucency measurements were greater than 3 mm in 28 of the cases (93.3%), and cystic hygroma was the most common detected abnormality (n: 22; 73.3%). All pregnancies with nonimmune hydrops resulted in abortion, intrauterine fetal death, or termination of the pregnancy.

Conclusion: Fetal hydrops diagnosed in the first trimester of gestation is associated with a higher incidence of aneuploidy, and it has a high mortality, even in fetuses with normal chromosomes.

Key words: Hydrops fetalis; First trimester; Nuchal translucency; Prenatal diagnosis.

Introduction

Fetal hydrops is defined as diffuse edema of the fetus and can be associated with many fetal conditions. The leading disorders that may be associated are fetal anemia, structural malformations, chromosome abnormalities, congenital infections, and metabolic defects [1]. This common symptom may be seen at any stage of gestation. Sonographic examination of the fetal nuchal anatomy at the end of the first trimester offers an opportunity for early screening of most aneuploidies and cardiovascular defects, to better understand the etiopathology of fetal hydrops. Although some causes of hydrops may be amenable to intrauterine treatment, the prognosis of non-immune fetal hydrops diagnosed in the first trimester of pregnancy is still unfavorable, probably related to its cause, and needs to be discussed.

The aim of this study was to review the etiology and outcome of 30 non-immune hydrops cases diagnosed in the first trimester of pregnancy, and to present our experience on pregnancies complicated by this condition.

Materials and Methods

Data was obtained from the records of 28 pregnancies with 30 fetuses with non-immune hydrops diagnosed before 14 weeks of gestation at the prenatal diagnosis unit of the University of Istanbul Medical Faculty between 1997 and 2000. The maternal and fetal records were reviewed for maternal age, gravidity, medical and pregnancy histories, reasons for referral for ultrasound examination, and ultrasound findings. Records were also reviewed for prenatal diagnostic procedures and laboratory results, including maternal blood group and serologic screening for toxoplasma gondii, rubella, cytomegalovirus, herpes simplex, and parvovirus B19. Inclusion criteria for non-immune fetal hydrops was defined as edema with effusion in at least one body cavity and skin edema or serous effusion in more than one body space in the absence of Rh isoimmunization. A detailed fetal anomaly scan was performed using 3.5-5 MHz transabdominal probes (Acuson 128XP, and Aloka 5500 SSD). The nuchal translucency thickness was measured and the presence of cystic hygroma, ascites and other effusions were noted. The fetal heart was evaluated for structural and rhythm abnormalities. Patients were offered karyotype analyzing by chorion villus biopsy or amniocentesis regarding the gestational age. Fetal karyotype results were obtained from the cytogenetic laboratory of our hospital. The fetal autopsy results were compared with ultrasound findings, when available. Outcomes of the pregnancies were obtained from the hospital records.

Results

Twenty-six pregnancies with 30 non-immune hydropic fetuses, including two sets of twins, were identified. Mean maternal age of the women was 25.8 (SD; ± 8.4) years and ranged from 16 to 47. Mean gestational age at the diagnosis was 12.9 (SD; ± 0.9) (range10.1 to 14.2). Sixteen (57.1%) of the 28 women were multiparous, and 11 of the multiparous women (68.7%) had had an adverse pregnancy outcome previously, including abortions, intrauterine fetal demises and anomalous fetuses. Six women had consanguinity (21.4%) with their partner. The main indications for referral were abnormal sonographic findings in a previous scan (n: 17), advanced maternal age (n: 6), consanguinity (n: 2), and fetal anomaly in previous pregnancies (n: 3). The two twin cases were monochorionic and both fetuses were similarly affected.

In sonographic examination all fetuses showed a degree of hydropic changes and 25 of them had additional abnormalities. Except for two cases, 28 of the 30 (93.3%) fetuses with hydrops had a nuchal translucency

Revised manuscript accepted for publication May 23, 2001

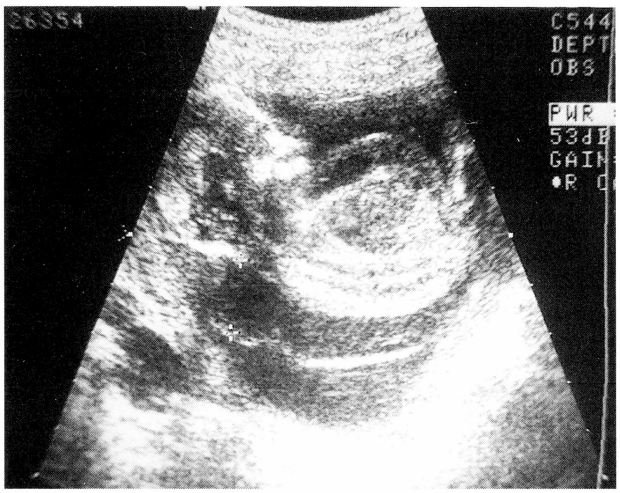

Figure 1. — Longitudinal appearance of a trisomy-18 fetus with hydrops at 14 weeks' gestation.

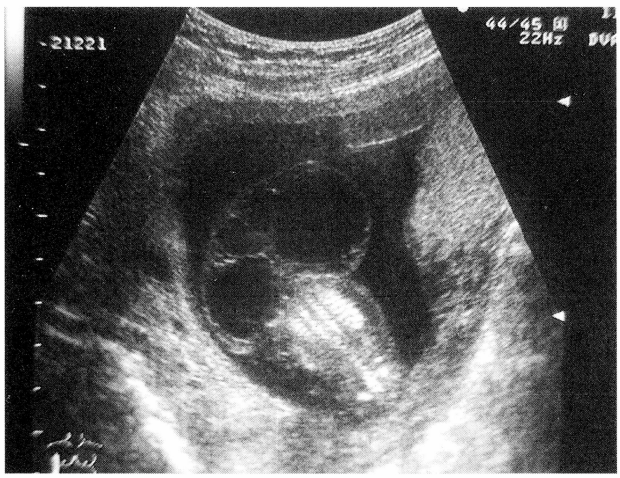

Figure 2. — Cystic hygroma. The dorsal view of the neck in a 13-week fetus with 45, X0.

measurement greater than 3 mm (Figure 1). Five of the affected fetuses had no abnormal findings other than skin edema and effusions. The type and frequency of abnormalities detected in the sonographic examination are shown at Table 1. The most frequent detected fetal abnormality was cystic hygroma (n: 22) (Figure 2).

Although invasive procedures were offered to all, parents did not desire further investigation in ten cases, and karyotype analyzing could be performed in only 20 of the 30 (66.6%) cases. Fifteen chorion villus samplings and five amniocenteses were performed, and except for one laboratory failure, karyotype results of 19 fetuses were obtained. Nine of the 19 fetuses (47.5%) showed chromosomal abnormality (Table 2). Turner syndrome was the most common chromosomal abnormality (n: 5), consisting of 26.3% of all karyotyped cases and 55.5% of abnormal results. The other chromosomal abnormalities detected were trisomy 21 (n: 2), and trisomy 18 (n: 2).

In 22 fetuses with cystic hygromas, 16 (72.7%) were analyzed and nine had abnormal chromosomes (9/16; 56.2%). All of the fetuses with abnormal karyotype had cystic hygromas. Five fetuses with cystic hygromas and normal karyotype had other structural malformations such as short extremities, kyphoscoliosis, and polycystic kidneys. Three fetuses free of cystic hygroma with unknown karyotype had structural abnormalities such as iniencephaly, short and deformed extremities, and urethral obstruction.

Among 28 pregnancies, although serologic evidence of maternal toxoplasmosis was detected in two cases, fetal infection could not be proved. Investigation for metabolic or other syndromes in selected cases did not result in specific diagnoses.

In 22 of 30 cases, pregnancy was terminated according to the desire of the parents (Table 3). Three of the gestations resulted in intrauterine fetal demise and two had spontaneous abortions during the investigation process. We could not obtain any information about the outcomes of three cases.

Autopsy results obtained in 11 of the cases showed some minimal discordance with prenatal ultrasound findings. Because the pregnancies were usually terminated before the 16th week (by surgical methods in some cases), or because of parental refusal, autopsy could not be performed in all cases.

Table 1. — *Type and number of abnormalities detected in 30 non-immune hydropic fetuses.*

Type of anomaly	N
Cystic hygroma	22
Talipes	3
Short and deformed extremities	1
Kyphoscoliosis	1
Iniencephaly	1
Encephalocele	1
Atrioventricular septal defect (AVSD)	1
Mid-facial cleft	1
Single umbilical artery	1
Urethral obstruction	1
Polycystic kidneys	1

Table 2. — *Chromosomal structure of the 19 fetuses with non-immune hydrops in the first trimester.*

Karyotype	N: 19	%
Normal	10	52.6
Abnormal	9	47.4
Turner (45 X0)	5	26.3
Trisomy 21	2	10.5
Trisomy 18	2	10.5

Table 3. — *Outcomes of the pregnancies diagnosed with fetal non-immune hydrops in the first trimester.*

Outcome	N: 30	%
TOP*	22	73.3
IUMF**	3	10.0
Spontaneous Abortion	2	6.7
Unknown	3	10.0

*TOP: Termination of the pregnancy; **IUMF: Intrauterine fetal death.

Discussion

Many prenatal diagnosis centers are now employing fetal nuchal translucency measurements to assess the risk of chromosomal abnormalities [2-4]. With the practice of this "first trimester screening", an increased number of fetal abnormalities can now be diagnosed by ultrasound examination in early pregnancy [5]. Not surprisingly, the mean gestational age at diagnosis of hydrops has fallen in recent years. As hydrops has been defined as a pathologic increase of interstitial and total fetal body fluid, an increase of the nuchal translucency thickness is probably the first stage of fetal hydrops.

Abnormalities of the fetal neck can be diagnosed as early as 9 weeks' gestation [6]. An increased nuchal translucency thickness is found in more than 80% of trisomic fetuses between 10 and 14 weeks' gestation [7]. In our study, 28 of 30 fetuses (93.3%) presented with a nuchal fold thickness of more than 3 mm, suggesting that nuchal abnormalities account for an important proportion of fetal hydrops cases in early pregnancy. The ultrasound differential diagnosis between increased nuchal translucency and cystic hygroma is not clear. However, many authors do not distinguish in early pregnancy between simple nuchal edema and nuchal cavitation resulting from an abnormality in the development of the lymphatic system.

There are several studies suggesting that cases of non-immune hydrops diagnosed at an early gestational age have a higher incidence of abnormal fetal karyotype and a higher perinatal mortality rate [8]. Our results are consistent with previous studies where we detected a 47.4% aneuploidy rate in karyotyped cases. The prevalence of chromosomal abnormalities in hydrops between 24 and 29 weeks of gestation are observed in 15.7% of cases according to the reports [10]. The incidence is higher at 11-17 weeks, suggesting that generalized skin edema has a high positive predictive value as a marker of aneuploidy and related fetal anatomical defects in early pregnancy [8].

Trisomy 21 and monosomy X are the most frequently identified chromosomal disorders related to fetal hydrops [11]. Trisomy 18, trisomy 13, and trisomy 16 are also common [11]. The spectrum of chromosome abnormalities was similar in our series showing a preponderance of monosomy X. Although we were not able to obtain karyotypes in all cases, the high prevalence of chromosome abnormalities in our study supports the suggestions of previous studies for karyotyping.

Some authors have suggested that there is a difference in the risk for fetal aneuploidy when septations are detected within the cystic nuchal lesion as opposed to lesions without septations [12-14].

Shulman *et al.* demonstrated "space-suit" fetal hydrops in the first trimester indicates an even higher risk of chromosome abnormalities than those observed among fetuses with isolated prominent nuchal translucency [9]. Nine of the fetuses (56.2%) with cystic hygromas among karyotyped cases had abnormal chromosomes in our study. On the other hand, all of the fetuses with abnormal karyotype had cystic hygromas. The frequency of monosomy X was highest (55.5%). This is consistent with the findings of the same study where the authors suggested that the ratio of sex chromosome to autosome cytogenetic abnormalities is considerably greater among fetuses with space-suit hydrops than among fetuses with isolated prominent nuchal translucencies [15].

Although hydrops with cystic hygroma has an increased risk for fetal cytogenetic abnormalities compared with isolated prominent nuchal translucency, the management of pregnancies with either abnormality is similar.

As the presence of associated abnormalities, such as holoprosencephaly or omphalocele, allows the differential diagnosis, a detailed sonographic examination is recommended in cases of non-immune fetal hydrops. We detected an atrioventricular septal defect (AVSD) in one fetus with trisomy 21. On the other hand, abnormalities of the heart and great arteries have been found with a higher incidence in chromosomally normal fetuses with increased nuchal thickness at 11-14 weeks [16]. Although the detection rate of fetal abnormalities in the first trimester is improving with the advances in technology and experience, it is still not easy to diagnose many malformations, especially of cardiac origin. If pregnancy is allowed to continue in the presence of a fetus with increased nuchal translucency and a normal karyotype, a detailed sonographic examination especially focused on the fetal heart should be employed after 20 weeks of gestation. No pregnancy in our cases, was continued and we do not know the proportion of abnormalities missed in prenatal examination as autopsy results were obtained in only 11 cases.

Because cystic hygroma is often associated with generalized skin edema, it is not surprising that cystic hygroma was the most common abnormality detected in our cases. Cystic hygromas diagnosed between 9 and 14 weeks' gestation are associated with up to a 60% risk of aneuploidy, with monosomy X being the most common abnormality [17]. The cases presenting with cystic hygromas and normal karyotype may have other dysmorphic sequela such as Noonan or Roberts syndrome, in which the diagnosis is based solely on clinical characteristics. [17]. Although Rh isoimmunization and other diseases characterized with anemia are accepted as one of the major causes of fetal hydrops, this is not valid for the first trimester. In general, these disorders have a slow development and usually show symptoms later. Homozygous α-thalassaemia-1 causes hydropic changes in only 7% of the cases investigated before 15 weeks of gestation [18]. Similarly, congenital infections such as human provirus B19 are less likely to be associated with fetal hydrops in early pregnancy. The association with infectious causes and fetal hydrops at 10-14 weeks was only 1.4% in a recent study compared with 9.5% in later affected pregnancies [19]. Although we found serologic evidence of maternal toxoplasma gondii infection in two cases, we were not able to demonstrate the fetal infection. Similarly, we could not diagnose any kind of specific syndromes or metabolic diseases in investigated cases, although the possibility of frequency may be higher in our population where the incidence of consanguinity and history of adverse pregnancy outcome were high.

The prognosis of fetal hydrops depends on the underlying etiology. Cardiac structural abnormalities, thoracic tumors, pleural effusion, and diaphragmatic hernia are usually associated with poor prognosis, with a perinatal mortality rate of 80-100% [10, 20]. If there are no major fetal abnormalities or chromosomal defects the prognosis is better because intrauterine therapy may provide reversal of hydrops and survival in some causes of non-immune fetal hydrops [10, 20]. However, no fetus survived in our cases in this earlier gestational period. Intrauterine therapy may aid survival in more advanced gestations, in which the incidence of chromosomal abnormalities is much lower.

Conclusion

Fetal hydrops diagnosed in the first trimester of gestation is associated with a higher incidence of aneuploidy and it has a high mortality, even in fetuses with normal chromosomes.

References

[1] Manchin G. A.: "Hydrops revisited: literature review of 1,414 cases published in the 1980s". *Am. J. Med. Genet.*, 1989, *34*, 366.
[2] Nicolaides K. H., Azar G., Byrne D., Mansur C., Marks K.: "Fetal nuchal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy". *BMJ*, 1992, *304*, 867.
[3] Sherer D. M., Manning F. A.: "First-trimester nuchal translucency screening for fetal aneuploidy". *Am. J. Perinatol.*, 1999, *16*, 103.
[4] Spencer K., Spencer C. E., Power M., Moakes A., Nicolaides K. H.: "One stop clinic for assessment of risk for fetal anomalies: a report of the first year of prospective screening for chromosomal anomalies in the first trimester". *BJOG*, 2000, *107*, 1271.
[5] Nicolaides K. H., Heath V., Liao A. W.: "The 11-14 week scan". *Baillieres Best Pract. Res. Clin. Obstet. Gynaecol.*, 2000, *14*, 581.
[6] Ville Y., Lalondrelle C., Doumerc S., Daffos F., Frydman R., Oury J. F.: "First trimester diagnosis of nuchal anomalies: Significance and fetal outcome". *Ultrasound. Obstet. Gynecol.*, 1992, *2*, 314.
[7] Pandya P. P., Kondylos A., Hilbert L., Snijders R. J. M., Nicolaides K. H.: "Chromosomal defects and outcome in 1015 fetuses with increased nuchal translucency". *Ultrasound. Obstet. Gynecol.*, 1995, *5*, 15.
[8] Iskaros J., Jauniaux E., Rodeck C.: "Outcome of nonimmune hydrops fetalis diagnosed during the first half of pregnancy". *Obstet. Gynecol.*, 1997, *90*, 321.
[9] Shulman L. P., Phillips O. P., Emerson D. S., Felker R. E., Tharapel A. T.: "Fetal 'space suit' hydrops in the first trimester: differentiating risk for chromosome abnormalities by delineating characteristics of nuchal translucency". *Prenat. Diagn.*, 2000, *20*, 30.
[10] Jauniaux E., Van Malgerdem L., De Munter C., Moscoso G., Gillerot Y.: "Non-immune hydrops fetalis associated with genetic abnormalities". *Obstet. Gynecol.*, 1990, *75*, 568.
[11] Van Malderghem L., Jauniaux E., Fourneau C., Gillerot Y.: "Genetic causes of genetic hydrops". *Pediatrics.*, 1992, *89*, 81.
[12] Bernstein H. S., Filly R. A., Goldberg J. D., Golbus M. S.: "Prognosis of fetuses with cystic hygroma". *Prenat. Diagn.*, 1991, *11*, 349.
[13] Bronshtein M., Bar-Hava I., Blumenfeld I., Bejar J., Toder A., Blumenfeld Z.: "The difference between septated and non-septated nuchal cystic hygroma in the early second trimester". *Obstet. Gynecol.*, 1993, *81*, 683.
[14] Shulman L. P., Emerson D. S., Grevengood C., Felker R. E., Gross S. J., Phillips O. P., Elias S.: "High frequency of cytogenetic abnormalities in fetuses with isolated cystic nuchal lesions and normal karyotypes detected in the first trimester". *Am. J. Obstet. Gynecol.*, 1994, *171*, 1278.
[15] Sebire N. J., Snijders R. J. M., Brown R., Southall T., Nicolaides K. H.: "Detection of sex chromosome abnormalities by fetal nuchal translucency screening at 10-14 weeks". *Prenat. Diagn.*, 1998, *18*, 581.
[16] Hyett J. A., Moscoso G., Nicolaides K. H.: "Abnormalities of the heart and great arteries in first trimester chromosomally abnormal fetuses". *Am. J. Med. Genet.*, 1997, *69*, 207.
[17] Tauffer P. M. L., Anderson C. E., Johnson A., Heeger S., Morgan P., Wapner R. J.: "The natural history of euploid pregnancies with first-trimester cystic hygromas". *Am. J. Obstet. Gynecol.*, 1994, *170*, 1279.
[18] Lam Y. H., Ghosh A., Tang M. H. Y., Lee C. P., Sin S. Y.: "Second-trimester hydrops fetalis in pregnancies affected by homozygos α-thalassaemia-1". *Prenat. Diagn.*, 1997, *17*, 267.
[19] Sebire N. J., Bianco D., Snijders R. J., Zuckerman M., Nicolaides K. H.: "Increased fetal nuchal translucency thickness at 10-14 weeks: is screening for maternal-fetal infection necessary?". *Br. J. Obstet. Gynaecol.*, 1997, *104*, 212.
[20] McCoy M. C., Katz V. L., Gould N., Kuller J. A.: "Non-immune hydrops after 20 weeks' gestation: Review of 10 years' experience with suggestions for management". *Obstet. Gynecol.*, 1995, *85*, 578.

Address reprint requests to:
RECEP HAS, M.D.
9-10 Kısım B-18 Daire 52
34750 Atakoy, Istanbul (Turkey)