CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

Natural History of Fetal Trisomy 13 After Prenatal Diagnosis

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Manuscript Received: 17 December 2013; Manuscript Accepted: 11 September 2014

There are currently limited data describing the natural history and outcome for fetal trisomy 13 diagnosed prenatally. The aim of this study was to evaluate the fetal and neonatal outcome for pregnancies with an established prenatal diagnosis of fetal trisomy 13, and a parental decision for continuation of the pregnancy. To this end, the obstetric and neonatal outcome data for such pregnancies, diagnosed at two referral Fetal Medicine Centers, were retrospectively obtained and examined. During the study period, there were 45 cases of trisomy 13 diagnosed at both units, of which 26 (56%) continued with the pregnancy to its natural outcome. There were 12 intrauterine deaths in the cohort resulting in a rate of 46.2% of intrauterine lethality. Conversely, the live birth rate was 53.8%. For infants born alive, neonatal death on day 1 of life occurred in 78.6% of cases. The overall early neonatal mortality rate was 93%. There was one infant death at 6 weeks of age and no survival noted beyond this period. These data provide reliable information for parental counseling pertaining to risk of intrauterine death when trisomy 13 is diagnosed prenatally. These data also indicate that the survival outcome is worse than that previously accepted from studies of postnatal follow up of live born infants with this diagnosis.

Key words: fetal trisomy 13; fetal medicine; neonatal outcome

How to Cite this Article:
Barry SC, Walsh CA, Burke AL, McParland P, McAuliffe FM, Morrison JJ. 2015. Natural history of fetal trisomy 13 after prenatal diagnosis.
Am J Med Genet A 167A:147–150.

INTRODUCTION

Trisomy 13 is the third most common autosomal trisomy, after trisomies 21 (Down syndrome) and 18 (Edwards syndrome) with a birth prevalence in the region of 1 in 5,000 to 1 in 20,000 [Wylie et al., 1994; Vendola et al., 2010]. The poor prognosis that exists for infants born with trisomy 13, Patau syndrome, has been well recognized and documented over the last forty years [Magenis et al., 1968; Wylie et al., 1994; Vendola et al., 2010]. It is also apparent that the survival rates after livebirth for this condition have not changed greatly during that time period. While such survival rates vary between reports, they can be summarized in approximate terms as follows: 30–60% at 1 week, 20–40% at 1 month, and 3–10% at the end of 1 year [Magenis et al., 1968; Wylie et al., 1994; Vendola et al., 2010]. Survival beyond the period of infancy is rare.

What has changed dramatically during this period of time is the ability to diagnose trisomy 13 prenatally, using screening or clinically indicated ultrasound assessments, and invasive diagnostic testing such as chorionic villous sampling and amniocentesis [Moran et al., 2002; Irving et al., 2011]. This has resulted in an increase in the prenatal diagnosis of trisomy 13, and a concomitant reduction in the liveborn prevalence of this condition [Irving et al., 2011]. At the same time, there appears to be a significant increase in the prevalence of pregnancies with trisomy 13 in recent years, a factor which may be attributed to the steady increase in maternal age observed in many developed countries [Irving et al., 2011]. In addition, the range of anomalies which are seen with fetal trisomy 13 can be variable and even atypical [Petry et al., 2013]. As this is generally a lethal condition, prenatal diagnosis raises the option of termination of pregnancy. However, when confronted with this diagnosis prenatally, it is important to counsel parents accurately about the ultimate prognosis, and the

Conflict of interest: none.

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Article first published online in Wiley Online Library (wileyonlinelibrary.com): 22 October 2014
DOI 10.1002/ajmg.a.36824

likelihood of intrauterine, neonatal or infant death, or long-term survival. For the small number of women who elect to continue with the pregnancy, there are minimal data pertaining to pregnancy outcome following prenatal diagnosis. The information that is currently available is derived from reported survival data of cohorts of infants who were liveborn with this condition [Magenis et al., 1968; Wylie et al., 1994; Vendola et al., 2010]. Such survival data may not apply in a similar way to the fetus with trisomy 13 who is diagnosed prenatally.

We have recently demonstrated that the long-term survival implications of trisomy 18 diagnosed prenatally are worse than those reported for infants born alive with this syndrome [Burke et al., 2012]. A recent study, which included evaluation of natural outcome after prenatal diagnosis of three cases of trisomy 13, outlined the need for further studies on this topic [Lakovschek et al., 2011]. The aim of this study was to investigate the fetal and neonatal outcome for a cohort of pregnancies in which a prenatal diagnosis of trisomy 13 was confirmed, and a decision was made for continuation of the pregnancy.

MATERIALS AND METHODS

This is a retrospective review of prospectively collated data on all cases of fetal trisomy 13 diagnosed at two tertiary referral fetal medicine centers in the Republic of Ireland; Galway University Hospital, and the National Maternity Hospital, Dublin, between the years 2000–2011. The practice of routine fetal anomaly scanning was not prevalent during the early years of this study, and hence most cases were referred on the basis of a suspicion of fetal abnormality on a routine ultrasound scan. First trimester biochemical screening tests, or nuchal translucency scans were not routinely offered to all women during the time period of the study. After assessment, and confirmation of structural abnormality, the parents were counseled in relation to chorionic villous sampling or amniocentesis. Once the diagnosis was established, the prospective parents were advised of this, and referred back to the original clinician for further care. The referring clinician was provided with correspondence requesting the follow-up clinical details pertaining to the fetal and neonatal outcome. This was further pursued with repeat correspondence, and telephone communication. After exclusion of all pregnancies for which termination of pregnancy took place, those for which insufficient information was available, fetuses with mosaicism or translocation involving chromosome number 13, and multiple pregnancies, there were 26 singleton pregnancies managed conservatively to natural outcome with a prenatal diagnosis of trisomy 13. For statistical analysis, a Fisher's exact test was used for comparison of proportions between groups and a non-parametric independent sample *t* test was used to compare groups.

RESULTS

During the study period, there were 45 cases of trisomy 13 diagnosed at both units. Eight (18%) opted for termination of pregnancy, 11 (24%) were lost to follow up, and 26 (56%) continued with the pregnancy. The clinical data pertaining to the 26 pregnancies are outlined in Table I. Specifically, the ultrasound features leading to suspicion of aneuploidy, and the weeks of gestation at which karyotyping occurred confirming trisomy 13, are demonstrated in this table. In addition, for those pregnancies in which intrauterine death occurred, the gestation at which this diagnosis was made is shown. For live born fetuses, the gestation at delivery, and the duration of survival (i.e., timing of neonatal or infant death), are provided.

Second trimester (range 19–27 weeks) diagnosis occurred in 20 (77.9%) cases with the remaining 6 (22.1%) cases diagnosed in the third trimester (range 28–32 weeks). There were 12 intrauterine deaths in the cohort resulting in a rate of 46.2% of intrauterine lethality. The weeks of gestation at which the intrauterine deaths occurred are graphically demonstrated in Figure 1. Conversely, the live birth rate was 53.8% (14/26). There was no significant difference between the risk of intrauterine death and the possibility of a live birth occurring ($P = 0.18$). For infants born alive, neonatal death on day 1 of life occurred in 78.6% of cases (11/14). A further two cases (14.3%) died in the first week of life, resulting in an overall early neonatal mortality rate of 93%. There was one infant death at 6 weeks of age and no survival noted beyond this period.

In relation to maternal morbidity and obstetrical interventions, pre-eclampsia occurred in three pregnancies (11.5%) and cesarean was performed in four cases (15.3% of all pregnancies included, and 28.5% of all pregnancies with the fetus alive at time of delivery). The reason for one of these cesarean procedures was severe pre-eclampsia, two were performed for social reasons, and one for abdominal pain. All parturients for whom an intrauterine fetal death had occurred were delivered vaginally. There were no documented maternal morbidities as a result of ongoing pregnancies.

There were no obvious determining features to assist in predicting the likelihood of outcome of either intrauterine death or neonatal death for fetuses with confirmed trisomy 13. The median gestation at prenatal diagnosis in the cohort for whom intrauterine death occurred was 25.5 weeks, and that for the infants who were born alive was 22 weeks gestation ($P = 0.24$). All fetuses were diagnosed as having more than one major structural abnormality, and there was no specific pattern of abnormalities evident in those who had an intrauterine death in comparison to fetuses who were subsequently liveborn.

DISCUSSION

The diagnosis of fetal trisomy 13 in pregnancy causes significant distress for prospective parents. While it is clear that the long term prognosis is uniformly poor, hitherto, there is little in the way of published information with which to counsel parents in this situation accurately about possible natural outcomes for the fetus. In absolute terms, the prevalence of fetal trisomy 13 is low, and the proportion of women who elect to continue with the pregnancy in this situation is also very small. The main strengths of this study include the reasonable number of cases included, and the fact that it is focused on continuation of pregnancy.

It is apparent from the results provided here that the outcome for prenatally diagnosed trisomy 13 is such that approximately half of the pregnancies result in an intrauterine death, and a further half achieve a live birth. For those born alive approximately 80% die on day 1, and the early neonatal mortality rate within 1 week of life was greater than 90%. Including all diagnoses in this series (n = 26), 25

TABLE I. Antenatal Sonographic Abnormality, Gestation at Karyotyping and Time of Perinatal Death

	Gestation/weeks		
Ultrasound findings	**Karyotyping**	**Demise**	**Time of death**
Antenatal fetal death n = 12			
Dandy-Walker, cleft, ECF, strawberry, mild hydronephrosis	21	36 + 2	
Pleural effusion, holoprosencephaly,	28	29	
Hydronephrosis, cardiac defect	28	28	
IUGR, HLHS, cleft, holoprosencephaly	25	32 + 4	
Echogenic bowel/kidneys/echogenic cardiac focus/oligohydramnios, VSD, hypocerebellum	22	32	
Dandy-Walker, VSD, large NT	22	37 + 1	
Cleft, cardiac anomaly	21	22	
Hydronephrosis, cleft	19	30	
IUGR, echogenic kidneys, cleft	32	33 + 1	
Echogenic kidneys, semi lobar holoprosencephaly, cleft	28	40	
Exomphalos, a facial cleft, talipes and polyhydramnios. AEDF	34	36	
Facial cleft and echogenic kidneys, fists, holoprosencephaly	26	38 + 6	
Neonatal death			
Holoprosencephaly, cleft, VSD	20	36	1 hr
Holoprosencephaly, cleft, VSD	23	40	1 hr
Cleft, AVSD	27	27	0.5 hr
Small cerebellum, indeterminate genitalia, transposition, cleft, cardiac anomaly	22	36	3 days
Hydronephrosis, hypocerebellum, cleft VSD	21	41	6 hr
Echogenic kidneys/omphalocele/oligohydramnios, holoprosencephaly, cardiac anomaly	32	38 + 5	1 hr
Holoprosencephaly, cardiac anomaly	20	39	42 days
Strawberry, cleft, large NT	27	40	5 days
Hypoplastic cerebellum, cardiac defect, cleft	21	34	0.5 hr
Echogenic bowel, large NT, CPC's, cleft, cardiac anomaly	21	35	4 hr
Clenched fists, rocker bottom feet, cleft, abnormal 4 chamber view	22	32 + 6	1 hr
IUGR, proboscis, echogenic kidneys, VSD, semilobar holoprosencephaly	22	39 + 2	0.5 hr
IUGR, facial cleft, echogenic kidneys, banana cerebellum, ventriculomegaly, cleft, HLHS	21		2 hr
Enlarged echogenic kidneys, 2 v cord, rocker bottom feet, semilobar holoprosencephaly	25	32	1 hr

ECF, echogenic cardiac focus; IUGR, intrauterine growth restriction; HLHS, hypoplastic left heart syndrome; NT, neural tube; AEDF, absent end diastolic flow; VSD, ventricular septal defect; AVSD, atrioventricular septal defect; CPC, choroids plexus cyst.

infants or 96% were dead by the end of the early neonatal period, that is, in first week of life. These figures indicate that the survival outcome is generally worse for prenatally diagnosed fetuses as a group, than for neonates with trisomy 13 who were diagnosed postnatally [Magenis et al., 1968; Wylie et al., 1994; Vendola et al., 2010]. In this latter group, the survival data can be summarized as follows: 30–60% at 1 week, 20–40% at 1 month, and 3–10% at the end of 1 year [Magenis et al., 1968; Wylie et al., 1994; Vendola et al., 2010].

A recent publication [Wu et al., 2013] has reported even better survival rates than previously described. This latter report outlined a median survival time of infants with full trisomy 13 to be 10 days with 18% surviving 3 months and 8% surviving at least a year. It is therefore important that data obtained from a cohort of trisomy 13, fetuses diagnosed prenatally is used for counseling parents at the time of prenatal diagnosis, rather than follow up data on infants born alive with Patau syndrome who were diagnosed postnatally. This study has not attempted to explain why survival may be worse for prenatally diagnosed fetuses, but this may be partially due to natural demise that occurs in utero with congenital malformations, alongside the possibility that the extent or severity of structural malformations may be greater for those fetuses diagnosed prenatally.

While prenatal diagnosis of trisomy 13 is effective in Ireland, termination of pregnancy is legally permitted only when there is a significant threat to the life of the mother arising from continuation of the pregnancy. It is therefore apparent that termination of pregnancy is not permitted for the vast majority of cases of trisomy 13 diagnosed prenatally. For this reason, many women elect to travel to another jurisdiction (frequently the United Kingdom) to pursue termination of pregnancy in these circumstances. However a significant proportion of women elect to continue the pregnancy, because

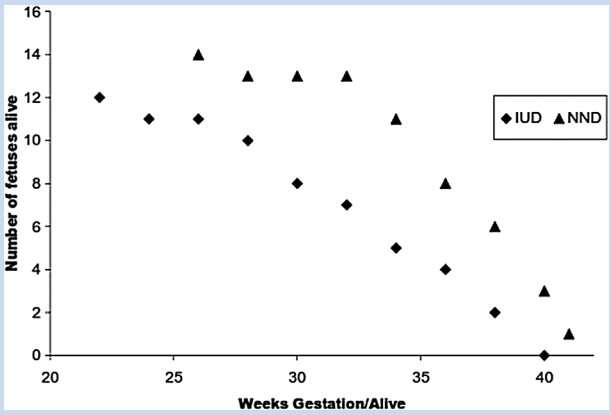

FIG I. Graphically demonstrates the weeks of gestation at which the intrauterine deaths occurred. IUD, Intrauterine death; NND, neonatal death.

of cultural or religious beliefs, and perhaps because the option of termination is not that easily accessible. Notwithstanding that, it is our view that the cases presented in this study are not biased in any way in terms of severity, or the lack of, in comparison to other cases of trisomy 13 diagnosed prenatally. They represent a random selection of cases for which the mother opted for continuation of the pregnancy. For infants born with trisomy 13 in Ireland, cardiopulmonary resuscitation is generally not performed and the neonatal care provided is very conservative and effectively palliative in nature. Such care is generally planned in a collaborative way between the obstetric team, the parents, and the neonatal pediatric team.

There are some limitations to this study. The study is a retrospective review of prospectively collected data. The majority of the diagnoses were made in the second trimester, but some were established in the third trimester. While trisomy 13 is most frequently diagnosed in the second trimester, it may also be diagnosed in the first trimester. There is no reason however to suspect that the outcome for fetuses with trisomy 13 diagnosed in the first trimester would be better, but may perhaps be worse. As a separate matter, while it is evident that women who elect to continue the pregnancy with a prenatal diagnosis of trisomy 13 are exposed to significant morbidity and obstetrical interventions, it is impossible to make reliable conclusions pertaining to the rates of such complications in these pregnancies from this current cohort size. What is not clear is whether or not the morbidity rate for pregnancies with a prenatally diagnosed trisomy 13 fetus, are different in comparison to when the fetus is of normal karyotype.

In conclusion, the results from this study outline the natural outcome for a moderately sized cohort of fetuses diagnosed prenatally with trisomy 13, and indicate that the survival outcome is worse than that previously accepted from studies of postnatal follow up of live born infants with this diagnosis. Finally, these data are useful when counseling parents who are faced with the prenatal diagnosis of trisomy 13.

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