

## Issues in prenatal counseling and diagnosis in Turner Syndrome

Melissa L. Loscalzo <sup>a,\*</sup>, Carolyn A. Bondy <sup>b</sup>, Barbara Biesecker <sup>c</sup>

<sup>a</sup> *Department of Pediatrics, University of South Florida, Tampa, FL, USA*

<sup>b</sup> *NICHD, NIH, Bethesda, MD, USA*

<sup>c</sup> *NHGRI, NIH, Bethesda, MD, USA*

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### Abstract

The advent of prenatal diagnosis in Turner Syndrome (TS) has brought with it challenges. Diagnosis may be prompted by characteristic abnormalities on prenatal ultrasound such as congenital heart disease and hydrops. Alternatively, diagnosis may be made incidentally on amniocentesis or chorionic villus sampling due to advanced maternal age. In cases of prenatal counseling, it is essential that counseling is provided by physicians and genetic counselors who are well-informed regarding TS and are aware of the current resources available. This chapter serves as a review of recent scientific literature regarding prenatal diagnosis in Turner Syndrome.

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*Keywords:* Prenatal diagnosis; X-chromosome; Hydrops; Ultrasound

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### 1. Prenatal detection

Turner Syndrome is caused by absence of all or part of one copy of the X chromosome. Postnatally, the diagnosis is generally prompted by characteristic clinical findings such as decreased linear growth, congenital heart anomalies, and lack of menarche and is confirmed by a peripheral blood karyotype. In contrast, the prenatal diagnosis of TS is often a more complex process and may be driven by abnormal findings on ultrasound or discovered as the result of routine chromosomal studies done for the indications of advanced maternal age or

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\* Corresponding author. 880 6th St. South, Suite 240; St. Petersburg, FL 33701, USA. Tel.: +1 727 767 8491; fax: +1 727 767 8270.

*E-mail address:* [mloscalz@hsc.usf.edu](mailto:mloscalz@hsc.usf.edu) (M.L. Loscalzo).

abnormal maternal serum screening. Particularly in the latter cases with normal ultrasound, outcome can be variable and difficult to predict.

### *1.1. Ultrasound*

The association of fetal nuchal cystic hygroma with Turner Syndrome has been well-described [1,2]. Often other characteristic anomalies such as aortic arch hypoplasia, short femurs, and renal anomalies are present and can be seen as early as 14 to 16 weeks gestation [3,4]. In a study of 19 European registries, 67.2% of prenatally diagnosed cases of Turner Syndrome were detected by abnormalities on ultrasound. 69.1% of cases had one anomaly present, and 30.9% had two or more anomalies [5]. Cystic hygroma was present in 59.5% of cases and hydrops in 19%. 81.6% of cases had a 45,X karyotype and 16.8% mosaic karyotypes. A subsequent study of 69 cases of TS diagnosed prenatally revealed similar results [4]. Of cases with a 45,X karyotype, 91% had shown one or more abnormalities on ultrasound prompting referral compared with 55.6% of mosaic cases. Cardiac defects were present in 13%, most commonly coarctation of the aorta (44.4%).

### *1.2. Maternal serum screening and advanced maternal age*

Turner Syndrome is not associated with advanced maternal age [6]. However, Turner Syndrome may be diagnosed incidentally in course of an amniocentesis or CVS performed for advanced maternal age or abnormal triple or quadruple maternal serum screen. Maternal serum screening may show a similar pattern to that suggestive of trisomy 21 or rarely trisomy 18 [7,8]. Outcomes of fetuses with Turner Syndrome prenatally ascertained on these bases can vary widely from those diagnosed based in ultrasonographic findings. These fetuses diagnosed by advanced maternal age or positive maternal serum screening are more often found to have a mosaic karyotype than those diagnosed based on ultrasonographic abnormalities, and conversely those with mosaic karyotypes are less likely to have associated ultrasound abnormalities [4]. Since the pursuit of prenatal diagnosis in such incidental cases generally is not prompted by concern about the presence, there may be little discussion regarding the possibility of TS or other sex chromosome abnormalities prior to testing. This presents further challenges in counseling parents about what the diagnosis will mean for their daughter, particularly in the absence of ultrasound abnormalities.

## **2. Karyotype and postnatal outcome**

Though maternal serum screening and ultrasound findings can be suggestive of TS, they are not diagnostic tests. Confirmation by karyotype through amniocentesis or chorionic villous sampling is mandatory. The specific karyotype of the fetus can also provide important information for counseling the family regarding potential prognosis for the fetus. Many conceptuses with a 45,X karyotype will miscarry. However, even those with anomalies on ultrasound can survive to term. Survival to term does not appear to correlate with the parent of origin of the X chromosome [9]. The presence of structural X anomalies or mosaicism for a 46,XX cell line is thought to have a protective effect on the fetus, decreasing fetal mortality and severity of the features [10]. Koeberl et al. [11] studied 12 girls with mosaic 45,X/46,XX

karyotypes diagnosed prenatally on amniocentesis for advanced maternal age or elevated maternal alpha-fetoprotein. These girls were compared with 41 postnatally diagnosed individuals. The patients diagnosed prenatally had milder clinical features and fewer childhood complications than those diagnosed postnatally. The severity was not related to the degree of mosaicism. All had normal growth, and only one had increased LH and FSH suggestive of ovarian dysfunction. This same difference in phenotypic severity does not appear to hold true for non-mosaic, 45,X, individuals diagnosed prenatally.

Gunther et al. [12] had similar findings in their study of 88 girls with TS. This study compared individuals diagnosed by traditional means (ultrasound anomalies or postnatal karyotype for clinic features) with those diagnosed incidentally (prenatal diagnosis for advanced maternal age or abnormal maternal serum screening). Those diagnosed incidentally had fewer phenotypic anomalies. Specifically, 64% of the individuals in the traditionally diagnosed group had cardiac anomalies in contrast to the incidentally diagnosed individuals in which a cardiac defect was present in 31%. Interestingly, there was no significant difference in the proportion with renal anomalies between the two groups. When subgrouped by karyotype, as expected, those with mosaic karyotypes had milder clinical features than those with a non-mosaic 45,X karyotype among both the incidental and traditional groups. Given this difference in prognosis for mosaic karyotypes, particularly those diagnosed incidentally, follow-up ultrasound examination and extended cytogenetic and molecular analyses to detect low level mosaicism can be helpful in cases of 45,X fetuses in with an initially normal ultrasound [13].

Finally, it is essential to remember that every test has a false positive rate, and some observations suggest that this may be a problem for incidental cytogenetic diagnoses of sex chromosome anomalies in the absence of clinical correlation [14,15].

### **3. Genetic counseling**

With the widespread availability of prenatal ultrasound and prenatal diagnosis by amniocentesis and chorionic villous sampling (CVS), a wide variety of individuals including obstetricians, nurses, geneticists, and genetic counselors are often involved in the process of prenatal diagnosis and discussion of test results. Because amniocentesis and CVS are often done for the indication of advanced maternal age or maternal marker screening, sex chromosome abnormalities may not be discussed in detail during pretest counseling. Few studies have systematically evaluated prenatal counseling in cases of TS. The outcome of counseling, the decision whether or not to terminate the pregnancy, seems at least in part to be determined by the nature of the information given and the expertise of the professional providing it. The results of a study by Robinson et al. [16] suggest that in cases of sex chromosome anomalies, parents who are counseled directly by a clinical geneticist are less likely to terminate a pregnancy.

A small pilot study by Hall et al. [17] of 23 pregnancies with sex chromosome abnormalities diagnosed prenatally found a direct correlation between the amount of negative information given by health professionals in the counseling process and the likelihood that the parents would choose to terminate the pregnancy. A more recent study of 61 couples with a prenatal diagnosis of a sex chromosome abnormality revealed that 100% chose to terminate a pregnancy with a 45,X karyotype [18]. Of those with a mosaic 45,X/46,XX karyotype, 2 of 4 were terminated. One of those terminated had been referred for anomalies on ultrasound. The

other mosaic cases were referred for advanced maternal age. These findings underscore the importance of detailed pretest and posttest counseling. It is essential that this counseling be provided by genetic counselors, geneticists, and endocrinologists who are highly familiar with TS. Discussion of prognosis should take into account the karyotype of the fetus in the context of ultrasound findings and the wide phenotypic spectrum associated with TS. Moreover, the medical professional should work in concert with organizations such as Turner Syndrome societies (e.g. [www.turner-syndrome-us.org](http://www.turner-syndrome-us.org)) that may connect the parents with other parents that have relevant experience.

## References

- [1] G. Azar, et al., Fetal nuchal cystic hygromata: associated malformations and chromosomal defects, *Fetal Diagnosis and Therapy* 6 (1–2) (1991) 46–57.
- [2] K. Nicolaidis, et al., Fetal nuchal oedema: associated malformations and chromosomal defects, *Fetal Diagnosis and Therapy* 7 (2) (1992) 123–131.
- [3] M. Bronshtein, E.Z. Zimmer, S. Blazer, A characteristic cluster of fetal sonographic markers that are predictive of fetal Turner Syndrome in early pregnancy, *American Journal of Obstetrics and Gynecology* 188 (4) (2003) 1016–1020.
- [4] C. Papp, et al., Prenatal diagnosis of Turner Syndrome: report on 69 cases, *Journal of Ultrasound Medicine* 25 (2006) 711–717.
- [5] N. Baena, et al., Turner Syndrome: evaluation of prenatal diagnosis in 19 European registries, *American Journal of Medical Genetics Part A* 129A (1) (2004) 16–20.
- [6] D. Warburton, et al., Monosomy X: a chromosome anomaly associated with young maternal age, *Lancet* 1 (8161) (1980) 167–169.
- [7] K. Wenstrom, R. Williamson, S. Grant, Detection of fetal turner syndrome with multiple-marker screening, *American Journal of Obstetrics and Gynecology* 170 (2) (1994) 570–573.
- [8] C. Ruiz, F. Lamm, P.S. Hart, Turner syndrome and multiple-marker screening, *Clinical Chemistry* 45 (12) (1999) 2259–2261.
- [9] A. Cockwell, et al., A cytogenetic and molecular study of a series of 45,X fetuses and their parents, *Journal of Medical Genetics* 28 (3) (1991) 151–155.
- [10] E. Hook, D. Warburton, The distribution of chromosomal genotypes associated with Turner's Syndrome: livebirth prevalence rates and evidence for diminished fetal mortality and severity in genotypes associated with structural X abnormalities or mosaicism, *Human Genetics* 64 (1983) 24–27.
- [11] D. Koeberl, B. McGillivray, V. Sybert, Postnatal diagnosis of 45,X/46,XX mosaicism and 45,X: implications for postnatal outcome, *American Journal of Human Genetics* 57 (3) (1995) 661–666.
- [12] D.F. Gunther, et al., Ascertainment bias in Turner Syndrome: new insights from girls who were diagnosed incidentally in prenatal life 10.1542/peds.2003-1122-L, *Pediatrics* 114 (3) (2004) 640–644.
- [13] B. Huang, et al., Prenatal diagnosis of 45,X and 45,X mosaicism: the need for thorough cytogenetic and clinical evaluations, *Prenatal Diagnosis* 22 (2) (2002) 105–110.
- [14] M. Griffiths, P. Miller, H. Stibbe, A false-positive diagnosis of Turner Syndrome by amniocentesis, *Prenatal Diagnosis* 16 (5) (1996) 463–466.
- [15] C.H. Gravholt, et al., Prenatal and postnatal prevalence of Turner's syndrome: a registry study, *BMJ* 312 (7022) (1996) 16–21.
- [16] A. Robinson, B. Bender, M. Linden, Decisions following the intrauterine diagnosis of sex chromosome aneuploidy, *American Journal of Medical Genetics* 34 (4) (1989) 552–554.
- [17] S. Hall, L. Abramsky, T. Marteau, Health professionals' reports of information given to parents following the prenatal diagnosis of sex chromosome anomalies and outcomes of pregnancies: a pilot study, *Prenatal Diagnosis* 23 (7) (2003) 535–538.
- [18] H.A. Hamamy, S. Dahoun, Parental decisions following the prenatal diagnosis of sex chromosome abnormalities, *European Journal of Obstetrics and Gynecology and Reproductive Biology* 116 (1) (2004) 58–62.