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Prenatal Diagnosis of 45,X/46,XX Mosaicism and 45,X: Implications for Postnatal Outcome

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Summary

The prognosis for 45,X/46,XX mosaicism diagnosed prenatally has yet to be established. We report our experience with 12 patients in whom prenatal diagnosis of 45,X/46,XX mosaicism was detected by amniocentesis for advanced maternal age or decreased maternal serum alpha-feto protein and compared them with 41 45,X/46,XX patients diagnosed postnatally. The girls in the prenatal group range in age from 3 mo to 10 years. All have had normal linear growth. Four had structural anomalies including: ASD (n = 1); ptosis and esotropia (n = 1); labial fusion (n = 1); and urogenital sinus, dysplastic kidneys, and hydrometrocolpos (n = 1). Gonadotropins were measured in seven; one had elevated luteinizing hormone/FSH at 3 mo of age. One has developmental delay and seizures as well as ophthalmologic abnormalities. None would have warranted karyotyping for clinical suspicion of Turner syndrome. The prevalence of 45,X/46,XX mosaicism is 10-fold higher among amniocenteses than in series of postnatally diagnosed individuals with Turner syndrome, which suggests that most individuals with this karyotype escape detection and that an ascertainment bias exists toward those with clinically evident abnormalities. The phenomenon of a milder phenotype for the prenatal group is similar to that observed for 45,X/46,XY diagnosed prenatally. Prenatal counseling for 45,X/46,XX in the absence of such ultrasound abnormalities as hydrops fetalis should take into account the expectation of a milder phenotype (except, possibly, with respect to developmental delay) than that of patients ascertained postnatally. The same does not hold true for 45,X diagnosed prenatally.

Introduction

Despite the fairly high frequency of 45,X/46,XX mosaicism among amniocenteses, the prognosis for this diagnosis has not been established. The frequency of 45,X/46,XX in a large series of amniocenteses, done for advanced maternal age or low maternal serum alpha-fetoprotein (MSAFP), was 1/3,000 (Wilson et al. 1989). However, few cases of liveborn individuals in whom 45,X/46,XX mosaicism was diagnosed prenatally have been reported (Kulkarni et al. 1989). The prevalence of 45,X/46,XX among patients with Turner syndrome is 8%–16%, or ~1 in 30,000 in the general population (Lippe 1991). Monosomy X is not associated with advanced maternal age (Warburton et al. 1980), and there is a lack of excessive prenatal mortality in 45,X/46,XX mosaicism, unlike that observed for 45,X (Hook and Warburton 1983). Presumably, therefore, only ~10% of 45,X/46,XX individuals are diagnosed postnatally. This apparently low rate of postnatal detection for 45,X/46,XX, coupled with the milder phenotype of individuals with 45,X/46,XY diagnosed prenatally compared with those diagnosed postnatally (Wheeler et al. 1988; Hsu 1989; Chang et al. 1990), suggested that the prenatal diagnosis of 45,X/46,XX mosaicism might predict a better prognosis than would a postnatal diagnosis. Therefore, we reviewed our patients diagnosed prenatally or postnatally with 45,X/46,XX or 45,X.

Patients, Material, and Methods

Twelve patients were diagnosed prenatally with 45,X/46,XX mosaicism (table 1). Ascertainment was for advanced maternal age (n = 7), decreased MSAFP (n = 2), hydrops fetalis in a twin who died in utero (n = 1), family history of Down syndrome (n = 1), and recurrent pregnancy losses (n = 1). Eleven patients were diagnosed prenatally with 45,X. These patients were ascertained for advanced maternal age (n = 5), decreased MSAFP (n = 1), or an ultrasound abnormality (n = 5). All were referred to the University of British Columbia, Vancouver, Canada, or Children's Hospital and Medical Center Medical Genetics clinics, Seattle, Washington, either for prenatal counseling and/or for postnatal evaluation. Patients in the postnatally diagnosed 45,X/46,XX and 45,X groups are participants in a long-term clinic for the study of the natural history of Turner syndrome at Children's Hospital and Medical Center. Evaluation of all patients included physical examinations, and many

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Table 1

Clinical Information for Prenatally Diagnosed Mosaic Patients

Patient	Age at Last Follow up	Clinical Features	FSH/LH (Age)	Karyotype[a]		
				Amnio	Blood (Age)	Skin
1	7 mo	Normal	Normal (7 mo)	19/30	14/25	ND
2	10 mo	Normal	Normal (1 mo)	11/17	5/20	ND
3[b]	1 year 9 mo	Normal	Normal (7 mo)	ND	9/48 (birth) 11/20 (7 mo)	0/51
4	2 years	Dysplastic kidney Urogenital sinus Hydrometrocolpos	Normal (2 years)[c]	6/29	0/27	0/850
5	3 years	Normal	ND	26/62	4/25	ND
6	4 years	Normal	Normal (6 mo)	2/28	0/50	0/24
7	4 years 8 mo	Atrial septal defect	Normal × 2 (2 mo; 3 years)	9/35	4/62	ND
8	6 years 2 mo	Normal	Elevated (3 mo)	40/56	4/100	ND
9	7 years 2 mo	Normal	Normal (3 mo)	13/50	0/50	6/50
10	9 years	Labial fusion	ND	12/40	0/100	ND
11	9 years 3 mo	Normal	ND	6/100	7/100	ND
12	9 years 11 mo	Developmental delay; seizures; ptosis	ND	16/24	12/43	ND

NOTE.—ND = Not done.

[a] No. of 45,X/total no. of cells.

[b] Twin died in utero with cystic hygroma. Patient delivered at 33 w. No amniocentesis. Possible chimera.

[c] Workup for premature thelarche. Normal FSH response to HCG stimulation. LH normal.

patients have had complete cardiac and renal evaluations, including cardiac and renal ultrasounds. Assays of the gonadotropins, FSH and luteinizing hormone (LH), were obtained when possible in the prenatally diagnosed group. Skeletal radiographs were obtained as indicated by the physical examination. Thyroid function studies were obtained as clinically indicated.

Peripheral blood karyotypes were analyzed for all patients with mosaicism and for six individuals with monosomy X. Confirmatory postnatal karyotyping was not performed in five, because they had clear-cut clinical features of Turner syndrome. Skin fibroblast karyotypes were analyzed for some patients.

Statistical analysis utilized the test statistic to assign *P* values when comparing two proportions (Altman 1991). Confidence intervals for the difference between two proportions were calculated as the standard error of the difference between the proportions to give the 95% confidence interval (Altman 1991). The two-sample *t*-test was used to compare two means (Altman 1991). We compared outcome based on prenatal versus postnatal diagnosis, in both 45,X and 45,X/46,XX.

Results

Individuals with a 45,X/46,XX Karyotype have a Milder Course If Diagnosed Prenatally

A series of 12 patients diagnosed with 45,X/46,XX mosaicism prenatally (prenatal) was compared with regard to clinical findings to a series of 41 45,X/46,XX individuals diagnosed postnatally (postnatal). The prenatal patients had less severe findings than the postnatal patients in the characteristics typically affected by Turner syndrome, including linear growth, ovarian function, and renal and cardiac anomalies (tables 2 and 3). All but three of the prenatal group had a completely normal appearance, and none would otherwise have warranted a chromosomal analysis for the suspicion of Turner syndrome.

Birth weight and length did not differ significantly between the two groups. The postnatal growth parameters of the prenatal individuals are normal, including growth velocity; all but one are above the fifth percentile for height, and that individual is just below the fifth percentile. We have prepubertal longitudinal growth data for 14 postnatal individuals. They uniformly fell below the fifth percentile for height before age 10 years. We have longitudinal measurements from early childhood for eight of these individuals, and, in all, short stature was evident before age 5 years. The majority of postnatal individuals are short. The mean final adult height for postnatal patients in our series (n = 12) is 149.2 cm, below the fifth percentile for adult women (Hamill et al. 1979). A minority of the postnatal patients have normal adult height. We predict that most of the prenatal patients will attain an adult height at or greater than the fifth percentile for normal adult females, on the basis of their current growth curves.

Table 2

Comparisons of Prenatally and Postnatally Diagnosed Individuals with 45,X and 45,X/46,XX

	Diagnosis			
	45,X (n = 201 − 2 terminations = 199)		45,X/46,XX (n = 56 − 3 terminations = 53)	
	Prenatal (n = 11)	Postnatal (n = 188)	Prenatal (n = 12)	Postnatal (n = 41)
Mean age now (years)	2.7 ± 1.8 (range 1–6)	18.5 ± 11.6 (n = 176) (range 0–75)	4.8 ± 3.3 (7 mo to 9 years 11 mo)	22.1 ± 14.5 (2 mo to 68 years)
Mean birth weight (kg)[a]	3.289 ± .417 (n = 7)	3.040 ± .522 (n = 137)	3.04 ± .415 (n = 7)	2.97 ± .482 (n = 25)
Mean birth length (cm)[a]	46.87 ± 3.5 (n = 6)	48.5 ± 3.1 (n = 104)	48.47 ± 2.4 (n = 6)	48.05 ± 2.4 (n = 17)
Prematurity	20% (2/10)	8.5% (15/175)	15% (2/13)	12% (4/34)
Mean age at diagnosis (years)	NA	7.2 ± 10 (n = 186)	NA	9 ± 9.8 (n = 38)
Reasons for diagnosis	45% advanced maternal age (n = 5); 27% cystic hygroma (n = 3); 9% decreased MSAFP (n = 1); 9% post fossa cyst (n = 1); 9% in utero edema (n = 1)	43% neonatal edema (n = 80); 27% short stature (n = 51); 13% 1° amenorrhea (n = 23); 7% 1° amenorrhea and short stature (n = 14); 3% unknown (n = 4); 7% other (n = 14)[b]	58% for advanced (n = 7) maternal age; 16% for decreased MSAFP (n = 2); 8% abnormal twin (n = 1); 8% family history of Down syndrome (n = 1); 8% recurrent pregnancy loss (n = 1)	5% edema (n = 2); 37% short stature (n = 15); 12% 1° amenorrhea (n = 5); 17% 1° amenorrhea and short stature (n = 7); 10% unknown (n = 4); 20% other (n = 8)[c]

NOTE.—n = total of individuals for whom information, either positive or negative, is available. NA = not applicable.

[a] Excludes premature infants.

[b] Comprises ambiguous genitalia (n = 1); multiple congenital anomalies (n = 1); oligohydramnios (n = 1); dysmorphic features (n = 3); developmental delay (n = 2); chronic lymphedema (n = 1); failure to thrive (n = 1); gastrointestinal bleeding (n = 1); premature aging (n = 1); abnormal ultrasound (n = 1); and webbing, coarctation (n = 1).

[c] Comprises multiple congenital anomalies (n = 1); dysmorphic features (n = 2); failure to thrive (n = 2); nuchal webbing (n = 1); multiple pregnancy losses (n = 1); and self-referral (n = 1).

Table 3

Comparison of Postnatal Medical Complications in 45,X and 45,X/46,XX: Prenatal versus Postnatal

	45,X (n = 201 − 2 terminations = 199)		45,X/46,XX (n = 56 − 3 terminations = 53)	
	Prenatal (n = 11)[a]	Postnatal (n = 188)[a]	Prenatal (n = 12)[a]	Postnatal (n = 41)[a]
Mental retardation[b]	9% (1/11)	11% (19/179)	8% (1/12)	8% (3/38)
Edema at birth	55% (6/11)	69% (112/163)	0	22% (7/31)
Nuchal webbing	45% (5/11)	52% (86/166)	0	29% (10/35)
Otologic problems[c]	77% (7/9)	77% (128/167)	17% (2/12)	53% (18/34)
Ophthalmologic problems[d]	33% (3/9)	35.5% (53/149)	8% (1/12)	20% (7/34)
Cardiac malformations[e]	37.5% (3/8)	44% (43/97)	12.5% (1/8)[f]	41% (7/17)
Renal abnormalities[e]	43% (3/7)	44% (59/133)	11% (1/9)	25% (5/20)
Gastrointestinal problems[g]	67.5% (5/8)	23% (35/153)	8% (1/12)	29% (9/31)

[a] Denominators given when information not available for the entire group.
[b] As measured by formal psychometric testing, need for total special education and/or institutionalization.
[c] e.g., recurrent otitis media, tympanostomy tubes.
[d] e.g., strabismus, ptosis, nystagmus.
[e] Includes only patients evaluated by echocardiogram, renal ultrasound, and/or intravenous pyelogram.
[f] Two had normal fetal cardiac ultrasounds and normal physical examinations postnatally; six had postnatal echocardiograms.
[g] e.g., feeding problems, failure to thrive, cleft lip ± cleft palate.

No evidence for early ovarian dysfunction was detected in 86% (6/7) of the prenatal mosaics tested. LH and FSH were assayed between 1 mo and 3 years of age. One had elevated values, indicating early ovarian dysfunction. An eighth patient had premature thelarche. FSH response to human chorionic gonadotropin (HCG) stimulation was normal, as was that of LH. Her serum estrogen levels were slightly elevated. Twenty-eight percent (8/29) of the adult postnatal patients have had spontaneous menses. Although the prevalence of ovarian dysfunction for the prenatally diagnosed 45,X/46,XX patients cannot yet be determined, as early ovarian failure may still occur, it is likely to be less than the 72% in the postnatally diagnosed mosaics.

Cardiac and renal anomalies were more common among 45,X/46,XX individuals diagnosed postnatally, but the differences were not statistically significant. Eight of 12 in the prenatal group were evaluated with an echocardiogram; the remaining four individuals had a normal cardiovascular examination without ultrasound confirmation. One patient (1/8, or 12.5%) in the prenatal group had a demonstrated cardiac anomaly, an atrial septal defect that ultimately closed spontaneously. Seven (41%) of 17 postnatal individuals who have had echocardiograms have had a structural cardiac anomaly; these included coarctations, aortic stenosis, and atrial septal defects (P = .1615). One (11%) of nine prenatal patients who underwent renal ultrasound evaluation had a renal anomaly, consisting of a dysplastic kidney accompanied by a urogenital sinus and hydrometrocolpos. Renal anomalies were detected by ultrasound evaluations in 25% (5/20) of postnatal patients who were evaluated, and included horseshoe kidney, duplication of the collecting system, and malrotation (P = .379).

Other complications associated with Turner syndrome in early childhood were more common among the postnatal group of 45,X/46,XX mosaics. Gastrointestinal problems, including failure to thrive, feeding difficulties, and cleft lip/cleft palate, occurred in 29% (9/31) of postnatal patients, compared with 8% (1/12) of prenatal patients (P = .2119). Prenatal patients had significantly fewer otologic problems (P = .0424, confidence interval .07–.63), and none had nuchal webbing or neonatal edema (P = .0332, confidence interval .14–.44; and P = .0784, respectively) (table 3). Ophthalmologic abnormalities that are detectable in early childhood, including strabismus and ptosis, were found in a similar proportion of each group (21% vs. 13%, P = .63). Congenital dislocation of the hip occurred in 4/31 (13%) of the postnatal group, but in none of the prenatal patients (P = .1902).

The proportion of 45,X cells on amniocentesis for the prenatal individuals varied from 7% to 71%. The proportion of 45,X lymphocytes on postnatal testing was <60% for all prenatal patients and <30% in all but two. We have information for 36 postnatal patients regarding the proportion of 45,X cells to 46,XX cells. Sixteen (44%) had >50% monosomy X cells; 6 (17%) had <50% and >30% monosomy X cells, and in 14 (39%), <30% of the cells were 45,X. These numbers are too small to allow for conclusions regarding the proportion of monosomy X cells as a predictor of outcome in the postnatal group. A second note of caution is struck in regard to trying to predict phenotype on the

basis of the proportion of 46,XX cells, by the patient in whom the proportion of 45,X cells in blood was 19% at birth but 55% at 7 mo. This suggests that differences in the proportion of abnormal cells may occur because of in vitro and in vivo stochastic events and that differences between patients may not be any more meaningful than fluctuations within an individual over time.

Only one of the prenatal individuals had anomalies that would have prompted karyotype analysis. Intellectual development is delayed in one individual (8%). The postnatal mosaic patients had an array of clinical findings that prompted karyotype analysis (table 2). Eight percent (3/38) have mental retardation. The risk for intellectual handicap does not appear to differ between postnatal and prenatal individuals, but the number of affected individuals in each group is small.

Prenatal Diagnosis Does Not Predict a Better Prognosis for Nonmosaic 45,X Individuals

The prenatally diagnosed 45,X individuals were not significantly different from the postnatally diagnosed 45,X individuals (tables 2 and 3). The majority (55%, or 6/11) were ascertained by ultrasound abnormalities, not during routine amniocentesis for advanced maternal age. Peripheral blood karyotyping to confirm the amniocentesis findings was done in only six, five of whom showed only 45,X cells in blood. One showed mosaicism for a 46,XX cell line in blood; 10/50 lymphocytes were 45,X. Four of 24 cells derived from her chorion were 45,X; all 16 cells analyzed from the amnion were 45,X. The patient had normal FSH and LH at age 6 mo and mild intrauterine growth retardation, but has had normal growth since and a normal cardiac echo and normal renal ultrasound.

Discussion

Prenatal counseling for 45,X/46,XX mosaicism should reflect the apparently better prognosis for the majority of these individuals, with appropriate caveats. A different course was observed for 45,X/46,XX mosaicism diagnosed prenatally compared to a postnatal diagnosis. The source of this difference is most likely a bias of ascertainment stemming from the indication for obtaining a karyotype in each situation. Postnatal recognition of mosaicism for Turner syndrome requires some abnormality to bring a patient to medical attention and to provide an indication for obtaining a karyotype. The prenatally diagnosed mosaic group was ascertained coincidentally when karyotyping was performed for advanced maternal age, or another indication unrelated to Turner syndrome (Warburton et al. 1980). The prenatally diagnosed group probably represents the phenotype of the majority of 45,X/46,XX individuals, in whom no indication for karyotyping is present postnatally. Conversely, the prenatally diagnosed 45,X group came to amniocentesis because of structural abnormalities in 55%. Thus it is not surprising that the phenotype of these individuals is similar to that for 45,X individuals diagnosed postnatally. It remains to be seen whether those 45,X individuals ascertained prenatally for advanced maternal age alone will have a milder postnatal phenotype.

Only one of eight prenatally diagnosed mosaics tested had elevated gonadotropins suggestive of ovarian failure. In the only other published data (Lippe et al. 1993), none of three neonates who were diagnosed prenatally with 45,X/46,XX had elevated gonadotropins. These results and ours must be interpreted with caution. First, the number of patients is small. Second, premature ovarian failure and/or ovulatory dysfunction is a well-recognized complication in individuals with Turner syndrome who have spontaneous puberty and menarche. Thus, while the normal gonadotropin levels in these patients are encouraging, assurance cannot be given of maintenance of ovarian function and normal fertility as adults.

A milder phenotype has similarly been observed when 45,X/46,XY mosaicism is diagnosed prenatally (Wheeler et al. 1988; Hsu 1989; Chang et al. 1990). A comparison of individuals with prenatally or postnatally diagnosed 45,X/46,XY revealed predominately normal male phenotypes among the prenatally diagnosed group, compared with a female or ambiguous male genitalia phenotype among the postnatally diagnosed group (Wheeler et al. 1988) and has influenced genetic counseling. Caution, again, must be exercised in promising or guaranteeing a normal outcome. A low incidence of genital anomalies among the prenatally diagnosed 45,X/46,XY individuals has been demonstrated subsequently (Hsu 1989; Chang et al. 1990), and the functional fertility of males with 45,X/46,XY cannot be confirmed until this group reaches adulthood.

LH and FSH should be measured in all infants diagnosed prenatally or postnatally with 45,X/46,XX Turner syndrome. As the levels of these gonadotropins are very low in cord blood and high in the first few weeks of life (Winter and Faiman 1972; Winter et al. 1975; Conte et al. 1980), testing should be done after several months of age. Although LH and FSH levels remain high throughout childhood in patients with gonadal dysgenesis (Winter and Faiman 1972), they begin decreasing by age 2 and approach closer to normal levels in childhood (age 5–10 years). Therefore, testing should be done prior to age 2 if possible. Although normal levels may not promise fertility, elevated levels guarantee the need for ovarian hormone replacement and allow for realistic planning of future medical care.

Growth failure in Turner syndrome is recognizable early in childhood. We are convinced that the normal growth rate and normal height for age in the prena-

tally diagnosed group promise normal or near-normal adult height and are less cautious in our optimistic predictions for this feature than we are for predictions of fertility.

The prenatal diagnosis of 45,X/46,XX is not necessarily benign. Although the numbers are small, the risk for mental retardation appears to be similar in both groups. As many couples in this counseling situation have had amniocentesis to detect Down syndrome, presumably they are most concerned about the risk for a mentally handicapped child. Thus, our inability to reassure them regarding this specific finding may prove problematic. Hopefully, larger series of prenatally diagnosed mosaics will further refine these risks.

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