ELECTRONIC LETTER

Physical and psychomotor development of 1799 children born after second trimester amniocentesis for maternal serum positive triple test screening and normal prenatal karyotype

I Witters, P Moerman, A Van Assche, J-P Fryns

J Med Genet 2002;**39**:e75(http://www.jmedgenet.com/cgi/content/full/39/12/e75)

In a previous retrospective study on the physical and psychomotor development of 868 children born after positive maternal serum triple test screening with normal prenatal karyotype, we found an increased incidence of complex multiple congenital anomalies syndromes (1.95%).[1]

In the present retrospective study, we collected data on 1799 children born after a pregnancy with a positive maternal serum triple test screening and normal prenatal karyotype and also found in these children an increased incidence of complex multiple congenital anomalies syndromes (23, 1.28%), with a total incidence of major congenital anomalies of 37.3%.

MATERIAL AND METHODS

During the period from 1 January 1996 to 31 December 1999, 2378 women had amniotic fluid analysed for aneuploidy based on a positive maternal serum triple test (risk for trisomy 21> or = 1/250). In Belgium, triple test screening is routinely offered to all pregnant women. These samples were analysed at the Leuven Centre for Human Genetics and showed normal chromosome results and normal amniotic fluid alpha-fetoprotein. These samples did not include the samples analysed in the previous study between 1 January 1993 and 31 December 1995.

Maternal serum triple tests and amniocenteses were performed in different centres. In February 2001, a questionnaire (available on request) was mailed to the 2378 women with a list of questions about the outcome of pregnancy, the perinatal history, and the physical and psychomotor development of their children. In this questionnaire, parents also answered if a fetal malformation was diagnosed prenatally and if pregnancy was interrupted; 265 questionnaires were returned because the address had changed. Of the 2113 questionnaires that arrived, 1807 (85.5 %) were answered. These 1807 women gave birth to 1799 singletons (two spontaneous abortions, three twin pregnancies). Further medical information on affected children was also obtained from the obstetricians and paediatricians and only confirmed information was used.

Key points

- In a previous retrospective study on the outcome of 868 children born after positive maternal serum screening with normal prenatal karyotype, we found an increased incidence of complex multiple congenital anomalies syndromes (1.95%).
- We present the results of a second retrospective study on 1799 children born after positive triple test screening and normal prenatal karyotype.

Table 1 Types of isolated minor and major malformations

Minor malformations		
Cardiopathies, small	ASD	1
	VSD	3
Multiple cutaneous haemangiomata (single haemangioma not included)		5
Aniridia		1
Vitiligo		1
Congenital cataract		1
Malformed nose		1
Bilateral club feet		2
Preauricular appendix		2
Sacral dimple		3
Postaxial polydactyly		1
Bifid uvula		1
Hypospadias grade II		3
Syndactyly fingers II–III		1
Pectus carinatum		1
Torticollis		1
Branchial cyst		1
Total		29 (1.66%)
Major malformations		
Sensorineural deafness/autoimmune thrombocytopenia		1
Right congenital deafness		1
Congenital hypothyroidism with ectopic sublingual thyroid		1
Oesophageal atresia		1
Urological malformations		
PUJ stenosis		3
VUJ stenosis		1
Vesicoureteral reflux	Grade II	1
	Grade III–IV	9
Ureter duplex with partial multicystic kidney		1
Ureter duplex		1
Congenital chylothorax		2
Familial megalencephaly - hypotonia		1
Duane anomaly		1
Cardiopathies		
Critical pulmonary stenosis (PS)		1
Critical aortic stenosis (AS)		1
Double outlet right ventricle with ventricular septal defect (DORV-VSD)		1
Multiple atrial and ventricular septal defects (ASD-VSD)		1
Large atrial septal defect (ASD)		1
Ventricular septal defect (VSD)		7
TAPVU-ASDII-PPS		1
ASDII-VSD (single kidney)		1
Aneurysma vena of Galen		1
Macrocrania - bifrontal hygroma		1
Macrocrania - bilateral postaxial polydactyly		1
Cleft palate with bifid uvula		1
Cleft lip		1
Jejunal atresia/IgG2 defiency		1
Total		44 (2.45%)

Table 2 Diagnosis in the 23 children with complex malformations (1.28%)

	No
(A) Monogenic syndromes	
(1) Fragile X syndrome (OMIM 309550)	1
(2) Sturge-Weber syndrome (OMIM 185300)	1
(3) Tuberous sclerosis (OMIM 191100)	1
(4) Beckwith-Wiedemann syndrome (OMIM 13 650)	1
(5) Apert-acrocephalosyndactyly type I (OMIM 101200)	1
(6) Menkes syndrome (OMIM 309400)	1
(7) Kartagener syndrome (OMIM 244400)	1
(8) Poland syndrome with left cleft hand (OMIM 173800)	1
(9) Cystic fibrosis (OMIM 219700)	1
(10) Fumoryl acetoacetase deficiency (OMIM 276700) with Dandy-Walker malformation/arachnoidal cyst	1
(11) X linked agammaglobulinaemia (OMIM 300300)	1
(12) Rett syndrome (OMIM 312750)	1
(B) MCA/MR syndromes – sequences	
(1) MCA/MR syndrome with cardiopathy (VSD), bilateral pes equinovarus, facial dysmorphism, congenital torticollis	1
(2) VACTERL association with radial hypoplasia, asymmetrical scapulae, left kidney dysplasia, vertebral anomaly (S_3), low implanted thumbs	1
(3) Infant with lethargy, thrombocytopenia, anaemia, and fatty liver, medium-long chain acyl Co a dehydrogenase deficiency not confirmed	1
(4) Congenital diaphragmatic hernia (CDH) (right) with cystic renal dysplasia	1
(5) MCA/MR syndrome with craniosynostosis-cerebellar cyst-hydrocephalus	1
(6) Holoprosencephaly sequence with hypotelorism, median cleft lip and cleft palate	1
(7) Pierre-Robin sequence	1
(8) MR syndrome with olivopontocerebellar atrophy	1
(9) Progressive encephalopathy*	1
(10) MCA syndrome with agenesis of the corpus callosum, bilateral cleft lip, and clenched hands	1
(11) MR syndrome with cardiopathy (truncus arteriosus) and facial dysmorphism	1

*Same neurological syndrome in sister and brother.

RESULTS

Isolated minor (n=29, 1.66%) and major (n=44, 2.45%) congenital malformations were present in 73 children (4.11%, table 1) and multiple congenital anomalies (MCA) syndromes in 23 (1.28%, table 2). One-third of the isolated major malformations were cardiac malformations (14/44) and one other third urological malformations (16/44). Table 2 gives a description of the MCA/MR syndromes diagnosed in 23 children (1.28%), 12 MCA/MR syndromes with monogenic inheritance (table 2A) and 11 MCA syndromes/sequences of unknown aetiology (table 2B). Five of the 23 children (patients 4, 5, 6 , 10, and 11, table 2B) died in the perinatal period. Of the 18 surviving children, eight are moderately to severely mentally retarded (patients 1, 3, 5, 6, and 12 (table 2A) and patients 1, 8, and 9 (table 2B).

DISCUSSION

The high incidence (1.95%) of complex multiple malformation syndromes documented in our previous retrospective study on the prognosis of children born after second trimester amniocentesis for maternal serum positive triple test screening and normal prenatal karyotype is confirmed in the present study (1.28%). As in the first study, the long term outcome is unfavourable in more than 50% of these MCA/MR syndromes/sequences: 5/23 perinatal deaths and 8/23 moderately to severely mentally retarded. The overall incidence of major congenital malformations in this study was 3.73% (isolated major, n=44, 2.45%; MCA syndromes, n=23, 1.28%). This compares to the 3.9% incidence of structural defects and genetic syndromes found in the follow up of 4116 chromosomally normal pregnancies with fetal nuchal translucency above the 95th centile for crown-rump length.[2]

A positive triple screening test result seems to select a group of pregnancies at risk, not only for numerical chromosomal abnormalities, but also for multiple congenital anomaly syndromes of variable aetiology. These data need confirmation by a further prospective study.

REFERENCES

1 **Witters I**, Legius E, Devriendt K, Moerman P, Van Schoubroeck D, Van Assche A, Fryns JP. Pregnancy outcome and long term prognosis in 868 children born after second trimester amniocentesis for maternal serum positive triple test screening and normal prenatal karyotype. *J Med Genet* 2001;**38**:336-8.
2 **Souka AP**, Snijders RJ, Novakov A, Soares W, Nicolaides KH. Defects and syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10-14 weeks of gestation. *Ultrasound Obstet Gynecol* 1998;**11**:391-400.