The 11–13-week scan: diagnosis and outcome of holoprosencephaly, exomphalos and megacystis

K. O. KAGAN*†, I. STABOULIDOU*, A. SYNGELAKI*, J. CRUZ*‡ and K. H. NICOLAIDES*‡

*Harris Birthright Research Centre for Fetal Medicine, King's College Hospital and ‡Department of Fetal Medicine, University College Hospital, London, UK and †Department of Obstetrics and Gynecology, University of Tuebingen, Tuebingen, Germany

ABSTRACT

Objective *To determine the prevalence and outcome of fetuses with holoprosencephaly, exomphalos and megacystis diagnosed at 11–13 weeks of gestation.*

Methods *As part of a prospective screening study for trisomy 21 in singleton pregnancies at 11 + 0 to 13 + 6 weeks' gestation, transabdominal ultrasound examination was performed to diagnose holoprosencephaly, exomphalos and megacystis. Fetal karyotype and pregnancy outcome in fetuses with these defects were examined.*

Results *Screening was carried out in 57 119 pregnancies. The prevalence of holoprosencephaly, exomphalos and megacystis was 1 : 1298, 1 : 381 and 1 : 1632, respectively. Chromosomal abnormalities, mainly trisomies 18 and 13, were found in 65.9% of fetuses with holoprosencephaly, in 55.3% with exomphalos and in 31.4% with megacystis. There was spontaneous resolution of the defect by 20 weeks in 92.5% of euploid fetuses with exomphalos containing only bowel and in 90% of the euploid fetuses with megacystis and bladder length of ≤ 15 mm.*

Conclusions *A high proportion of fetuses with holoprosencephaly, exomphalos and megacystis diagnosed at 11–13 weeks of gestation are aneuploid, but in the majority of cases exomphalos and megacystis represent temporary abnormalities that resolve spontaneously. Copyright © 2010 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

A beneficial side effect of screening for trisomy 21 at 11–13 weeks of gestation is the early diagnosis of major fetal defects such as holoprosencephaly, exomphalos and megacystis. All three defects are associated with chromosomal abnormalities, especially with trisomies 18 and 13.

There are no screening studies reporting on the prevalence of holoprosencephaly in the first trimester of pregnancy. However, this defect was reported in 27% of 181 fetuses with trisomy 13 at 11–13 weeks of gestation[1]. At 11–13 weeks of gestation, fetal megacystis is defined by a longitudinal bladder diameter of ≥ 7 mm. In a first-trimester screening study involving 24 492 pregnancies, there was megacystis in 15 fetuses (a prevalence of 1 in 1633) and 20% of these had chromosomal abnormalities[2]. A study of 145 fetuses with megacystis reported that 30 (21%) had chromosomal abnormalities, mainly trisomies 13 and 18[3]. A screening study at 11–13 weeks of gestation, involving 15 726 pregnancies, reported exomphalos in 18 (a prevalence of 1 in 874), and 61% had chromosomal abnormalities, mainly trisomies 18 and 13[4]. Exomphalos at 11–13 weeks of gestation was observed in 26% of the 85 fetuses with trisomy 18[5] and in 28% of the 181 fetuses with trisomy 13[1].

We have recently reported on the development of specific algorithms for first-trimester screening for trisomy 21, trisomy 18 and trisomy 13, based on the combination of maternal age, fetal nuchal translucency (NT) thickness, fetal heart rate (FHR), maternal serum-free β-human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein-A (PAPP-A). When all three algorithms are used the estimated detection rates of trisomies 21, 18 and 13 are 91%, 97%, and 94%, respectively, for an overall false-positive rate of 3.1%[6].

The aims of this screening study involving 57 119 singleton pregnancies were, first, to determine the prevalence of holoprosencephaly, exomphalos and megacystis at 11–13 weeks of gestation, second, to compare the

ORIGINAL PAPER

estimated risk for trisomies 21, 18 and 13 in the chromosomally abnormal and euploid fetuses with these defects, and, third, to determine the outcome of affected pregnancies.

METHODS

This was a prospective screening study for trisomy 21 in singleton pregnancies, using a combination of maternal age, fetal NT thickness and maternal serum-free β-hCG and PAPP-A in a one-stop-clinic for first-trimester assessment of risk (OSCAR) at $11 + 0$ to $13 + 6$ weeks of gestation[7,8]. Transabdominal ultrasound examination was performed to diagnose any major fetal defects and to measure the fetal crown–rump length (CRL), NT thickness and FHR. Automated machines that provide reproducible results within 30 minutes were used to measure PAPP-A and free β-hCG (Delfia Express System; Perkin Elmer, Waltham, USA and Kryptor System; Brahms, Berlin, Germany).

Maternal demographic characteristics, ultrasonographic measurements and biochemical results were recorded in a computer database. Karyotype results and details on pregnancy outcomes were added to the database as soon as they became available. A search of the database was performed to identify all singleton pregnancies in which first-trimester combined screening was carried out from July 1999 to April 2007.

The diagnosis of alobar holoprosencephaly was based on the fusion of the anterior horns of the lateral ventricles and the absence of the butterfly sign in a cross-sectional view of the fetal brain[9]. Exomphalos was diagnosed if there was herniation of bowel or liver in the base of the umbilical cord and if the CRL was ≥ 45 mm. Megacystis was defined as enlarged bladder with a diameter of ≥ 7 mm[3].

Statistical analysis

We estimated the risk for trisomy 21, trisomy 18 and trisomy 13 by the combined test based on maternal age, fetal NT, FHR, free β-hCG and PAPP-A, and used the sum of all three risks to calculate detection and false-positive rates by taking the proportions with risks above a given risk threshold.[6]

RESULTS

Study population

The search of the database identified 60 172 singleton pregnancies. In 3053 (5.1%) cases, the outcome or one of the covariates was not available. Thus, our study population consisted of 57 119 pregnancies: 56 376 pregnancies with a normal karyotype or delivery of a phenotypically normal baby (unaffected group), 395 cases of trisomy 21, 122 cases of trisomy 18, 61 cases of trisomy 13, 38 cases with Turner syndrome and 127 cases with other chromosomal abnormalities. The

Table 1 Characteristics of the study population

Characteristic	Median (range) or n (%)
Maternal characteristics	
Age (years)	35.3 (14.1–52.5)
Weight (kg)	63.6 (34–165)
Spontaneous conception	54 456 (95.3)
Smoker	2583 (4.5)
Ethnicity	
Caucasian	51 025 (89.3)
Afro-Caribbean	2443 (4.3)
East Asian	644 (1.1)
South Asian	2229 (3.9)
Mixed	778 (1.4)
Gestational age	
11 + 0 to 11 + 6 weeks	5677 (9.9)
12 + 0 to 12 + 6 weeks	32 037 (56.1)
13 + 0 to 13 + 6 weeks	19 405 (34.0)
Crown–rump length (mm)	62.8 (45.0–84.0)
Karyotype	
Normal	56 376 (98.7)
Trisomy 21	395 (0.7)
Trisomy 18	122 (0.2)
Trisomy 13	61 (0.1)
Turner syndrome	38 (0.07)
Other	127 (0.2)
Total	57 119

characteristics of the study population are summarized in Table 1.

According to the maternal age distribution of our population and the gestational age at the time of screening we would have expected 367 (95% prediction interval 329–405) cases with trisomy 21, 112 (95% prediction interval 91–133) cases with trisomy 18 and 50 (95% prediction interval 36–64) cases with trisomy 13[10,11].

Holoprosencephaly

The prevalence of holoprosencephaly was 1 : 1298 (44 of 57 119). The fetal karyotype was normal in 15 (34.1%) and abnormal in 29 (65.9%), including 25 cases of trisomy 13 (Table 2).

In the chromosomally abnormal fetuses, compared with the euploid group, median maternal age, fetal NT and FHR were higher, and free hCG and PAPP-A were lower (Table 3). The estimated risk for trisomies based on maternal age, fetal NT, FHR, free β-hCG and PAPP-A was above 1 : 100 in 28 of the 29 (96.7%) chromosomally abnormal fetuses and in one of the 15 (6.7%) euploid fetuses.

In all cases with holoprosencephaly the pregnancy was terminated at the request of the parents.

Exomphalos

In the study population of 57 119 pregnancies, there were 150 (0.08%) cases with exomphalos, giving a prevalence of 1 : 381. However, the prevalence was dependent on the fetal CRL and the content of the exomphalos.

Table 2 Incidence of holoprosencephaly, exomphalos and megacystis in chromosomally normal and abnormal fetuses

			Chromosomal abnormality					
	n	Euploid	All	Trisomy 21	Trisomy 18	Trisomy 13	Turner	Other
Holoprosencephaly	44	15 (34.1)	29 (65.9)	—	1 (4.0)	25 (86.2)	—	3 (10.3)*
Exomphalos containing bowel only	133	59 (44.4)	74 (55.6)	3 (4.1)	42 (56.8)	19 (25.7)	6 (8.1)	4 (5.4)†
Exomphalos containing liver	17	8 (47.5)	9 (52.9)	—	6 (66.7)	3 (33.3)	—	—
Megacystis	35	24 (68.6)	11 (31.4)	1 (9.1)	4 (36.4)	6 (54.5)	—	—

Data are expressed as *n* or *n* (%). *Two cases of triploidy and one of 46,XX, add(6)(q26). †Three cases of triploidy and one of 46,XY, add(21)(p11.1).

Table 3 Characteristics of first-trimester combined test in euploid and aneuploid fetuses with holoprosencephaly, exomphalos and megacystis

	Holoprosencephaly		Exomphalos		Megacystis	
	Euploid (n = 15)	Aneuploid (n = 29)	Euploid (n = 67)	Aneuploid (n = 83)	Euploid (n = 24)	Aneuploid (n = 11)
Maternal age (years)	33.1 (30.2–36.6)	37.8 (35.3–40.4)	34.7 (31.8–37.0)	39.0** (36.0–40.8)	33.9 (30.7–36.1)	37.0 (35.6–39.0)
Delta NT (mm)	0.0 (−0.3 to 0.3)	2.7** (0.5–4.3)	0.1 (−0.1 to 0.7)	3.6** (1.4–5.2)	0.0 (−0.3 to 0.2)	1.3* (0.3–3.0)
Delta fetal heart rate (bpm)	0.6 (−4.9 to 4.4)	15.5** (10.6–21.1)	1.6 (−3.4 to 5.2)	1.7 (−5.6 to 15.5)	0.1 (−1.9 to 4.8)	11.2* (6.3–16.3)
PAPP-A (MoM)	0.90 (0.66–1.28)	0.21** (0.15–0.36)	0.96 (0.70–1.38)	0.29** (0.15–0.46)	0.99 (0.60–1.34)	0.19** (0.10–0.46)
Free β-hCG (MoM)	0.94 (0.61–1.55)	0.40* (0.28–0.59)	1.04 (0.63–1.63)	0.32* (0.18–0.57)	0.86 (0.59–1.15)	0.41* (0.18–0.41)
Median risk for trisomies	1:3433	1:2	1:2840	1:2	1:4800	1:4
Risk for trisomies > 1:100	1 (6.7)	28† (96.7)	11 (16.4)	80‡ (96.4)	1 (4.2)	11 (100)

Data are presented as median (interquartile range), ratio or *n* (%). Differences between aneuploid and euploid fetuses were tested using a *t*-test, and significant differences are indicated: *$P < 0.05$; **$P < 0.001$. †One case missed: 46,XX, add(6)(q26). ‡Three cases missed: two cases of triploidy and one case of 46,XY, add(21)(p11.1). hCG, human chorionic gonadotropin; MoM, multiples of the median; NT, nuchal translucency; PAPP-A, pregnancy-associated plasma protein-A.

For an exomphalos containing bowel only, the prevalence was 1:98 for a CRL of 45.0–54.9 mm, 1:798 for a CRL of 55–64.9 mm and 1:2073 for a CRL of 65.0–84.0 mm. The prevalence for an exomphalos containing liver was 1:3360. The fetal karyotype was abnormal in nine (52.9%) of 17 cases with an exomphalos containing liver and in 74 (55.6%) of 133 cases with an exomphalos containing bowel only (Table 2).

In the chromosomally abnormal fetuses, compared with the euploid group, median maternal age, fetal NT and FHR were higher, and free β-hCG and PAPP-A were lower (Table 3). The estimated risk for trisomies based on maternal age, fetal NT, FHR, free β-hCG and PAPP-A was above 1:100 in 80 of the 83 (96.4%) chromosomally abnormal fetuses and in 11 of the 67 (16.4%) euploid fetuses.

There were eight euploid fetuses with exomphalos containing liver, and in the four where the parents chose to continue with the pregnancy the condition persisted until delivery. There were 59 euploid fetuses with exomphalos containing only bowel. In three cases there was spontaneous miscarriage and in another three the pregnancies were terminated because of large fetal NT and generalized hydrops. In the remaining 53 continuing pregnancies, there were 49 (92.5%) cases with spontaneous resolution of the exomphalos by 20 weeks and the subsequent birth of healthy infants, and four cases where the condition persisted until delivery.

Megacystis

The prevalence of megacystis was 1:1632 (35 of 57 119). The fetal karyotype was normal in 24 (68.6%) cases and abnormal in 11 (31.4%) cases, including six with trisomy 13 and four with trisomy 18 (Table 2). In 31 of the cases with megacystis the bladder length was 7–15 mm and in four cases it was > 15 mm.

In the chromosomally abnormal fetuses, compared with the euploid group, median maternal age, fetal NT and FHR were higher, and free hCG and PAPP-A were lower (Table 3). The estimated risk for trisomies based on maternal age, fetal NT, FHR, free β-hCG and PAPP-A, was > 1:100 in all 11 chromosomally abnormal fetuses and in one of the 24 (4.2%) euploid fetuses.

In one of the 21 euploid cases with bladder length of ≤ 15 mm there was spontaneous miscarriage; in the remaining 20 cases there were 18 (90%) with spontaneous resolution of the megacystis by 16 weeks and the subsequent birth of healthy infants and two where there was evolution to obstructive uropathy (and these pregnancies were terminated). In the four cases with fetal megacystis of > 15 mm the pregnancies were terminated.

DISCUSSION

The findings of the study demonstrate that at 11–13 weeks of gestation, first, the prevalence of holoprosencephaly, exomphalos and megacystis is about 1 in 1300, 1 in 400 and 1 in 1600, respectively; second, these defects are associated with a high incidence of chromosomal abnormalities (mainly trisomies 18 and 13), found in about 65% of fetuses with holoprosencephaly, 55% with exomphalos and 30% with megacystis; and, third, in the majority of cases, exomphalos and megacystis represent temporary abnormalities that resolve spontaneously.

Our results on the prevalence of exomphalos and megacystis at 11–13 weeks of gestation and the proportion with chromosomal abnormalities are consistent with the results of previous smaller studies[2–4]. Mann *et al.* reported on a postnatal prevalence of exomphalos of 1 in 3000[12]. In our study, the prevalence of exomphalos containing only bowel varied between 1 in 98 and 1 in 2073, according to the CRL and in cases containing liver it was 1 in 3360. With respect to the aneuploidy rate and the high loss-rate of trisomic fetuses, our figures are in concordance with the reported postnatal incidence of 1 in 3000[12,13].

In the case of holoprosencephaly there are no previous screening studies at 11–13 weeks of gestation. A study from a population-based register of congenital abnormalities, involving 531 686 births between 1985 and 1998, estimated that the prevalence of holoprosencephaly in second-trimester pregnancies is about 1 in 8000, which is six times lower than in our study[14]. Possible explanations for this apparent discrepancy are poor ascertainment and under-reporting of affected cases in the registry and the high rate of intrauterine lethality during the early second-trimester of affected fetuses with trisomy 13[11]. A study involving pathological examination of 36 380 conceptuses, obtained through induced abortion before 10 weeks of gestation during the time-period 1962–1974, reported that the prevalence of holoprosencephaly was 1 in 240[15].

The diagnosis of holoprosencephaly, exomphalos or megacystis should constitute an indication for offering to the parents the option of fetal karyotyping. Because the prevalence of these defects is $< 0.1\%$, the effect on the overall proportion of pregnancies requiring an invasive test would be minimal. Effective screening for trisomies 21, 18 and 13 can be performed by a combination of maternal age, fetal NT, fetal heart rate, free β-hCG and PAPP-A. We have previously shown that by combining the three risk algorithms for trisomies 21, 18 and 13, the detection rate for trisomy 21 is about 90% and for trisomies 18 and 13 it is $> 95\%$, for an overall false-positive rate of 3.1%[6]. As demonstrated in our study, these algorithms will identify the vast majority of the chromosomally abnormal fetuses with holoprosencephaly, exomphalos or megacystis.

The outcome for fetuses with holoprosencephaly is fatal and only a few children survive the neonatal period, all of whom have a major developmental disability. In this respect, fetal karyotyping will not influence the common decision of parents in favor of pregnancy termination. The main aim of karyotyping is to define the risk of recurrence, which is $< 1\%$ if the karyotype is normal and $> 10\%$ if the karyotype is abnormal. The high risk of recurrence of holoprosencephaly in euploid fetuses is caused by the common association with several genetic syndromes, including Pallister Hall, Smith-Lemli–Opitz and CHARGE syndrome[16–18].

In contrast to holoprosencephaly, exomphalos containing liver and megacystis with bladder length > 15 mm (which are irreversible anatomical defects), megacystis with bladder length ≤ 15 mm and exomphalos containing only bowel are transient abnormalities. In such cases the parents can be reassured that once the fetal karyotype is found to be normal the conditions are likely to resolve spontaneously over the subsequent few weeks without any residual damage. Because in normal development exomphalos containing bowel only is observed in all fetuses at 8 weeks of gestation and subsequently resolves by 11 weeks, persistence at 11–13 weeks can be considered to be a delay in the recovery of physiological herniation of the bowel and such delay is more common in aneuploid than euploid fetuses. Similarly, megacystis at 11–13 weeks can be the consequence of developmental delay. The presence of smooth muscle in the bladder and autonomic innervation occur only after 13 weeks, and before this gestation time the bladder wall consists of epithelium and connective tissue with no contractile elements. It is therefore likely that in the majority of fetuses with megacystis there is no underlying urethral obstruction but a temporary malfunction of the bladder during a critical stage in its development[19].

REFERENCES

1. Papageorghiou AT, Avgidou K, Spencer K, Nix B, Nicolaides KH. Sonographic screening for trisomy 13 at 11 to 13 + 6 weeks of gestation. *Am J Obstet Gynecol* 2006; **194**: 397–401.
2. Sebire NJ, von Kaisenberg C, Rubio C, Snijders RJM, Nicolaides KH. Fetal megacystis at 10–14 weeks of gestation. *Ultrasound Obstet Gynecol* 1996; **8**: 387–390.
3. Liao AW, Sebire NJ, Geerts L, Cicero S, Nicolaides KH. Megacystis at 10–14 weeks of gestation: chromosomal defects and

outcome according to bladder length. *Ultrasound Obstet Gynecol* 2003; **21**: 338–341.

4. Snijders RJ, Sebire NJ, Souka A, Santiago C, Nicolaides KH. Fetal exomphalos and chromosomal defects: relationship to maternal age and gestation. *Ultrasound Obstet Gynecol* 1995; **6**: 250–255.

5. Sherod C, Sebire NJ, Soares W, Snijders RJ, Nicolaides KH. Prenatal diagnosis of trisomy 18 at the 10–14-week ultrasound scan. *Ultrasound Obstet Gynecol* 1997; **10**: 387–390.

6. Kagan KO, Wright D, Valencia C, Maiz N, Nicolaides KH. Screening for trisomies 21, 18 and 13 by maternal age, fetal nuchal translucency, fetal heart rate, free beta-hCG and pregnancy-associated plasma protein-A. *Hum Reprod* 2008; **23**: 1968–1975.

7. Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10–14 weeks of gestation. Fetal Medicine Foundation First Trimester Screening Group. *Lancet* 1998; **352**: 343–346.

8. Nicolaides KH, Spencer K, Avgidou K, Faiola S, Falcon O. Multicenter study of first-trimester screening for trisomy 21 in 75 821 pregnancies: results and estimation of the potential impact of individual risk-orientated two-stage first-trimester screening. *Ultrasound Obstet Gynecol* 2005; **25**: 221–226.

9. Sepulveda W, Dezerega V, Be C. First-trimester sonographic diagnosis of holoprosencephaly: value of the "butterfly" sign. *J Ultrasound Med* 2004; **23**: 761–765.

10. Cuckle HS, Wald NJ, Thompson SG. Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and serum alpha-fetoprotein level. *Br J Obstet Gynaecol* 1987; **94**: 387–402.

11. Snijders RJM, Sebire NJ, Cuckle H, Nicolaides KH. Maternal age and gestational age-specific risks for chromosomal defects. *Fetal Diagn Ther* 1995; **10**: 356–367.

12. Mann S, Blinman TA, Douglas Wilson R. Prenatal and postnatal management of omphalocele. *Prenat Diagn* 2008; **28**: 626–632.

13. Lakasing L, Cicero S, Davenport M, Patel S, Nicolaides KH. Current outcome of antenatally diagnosed exomphalos: an 11 year review. *J Pediatr Surg* 2006; **41**: 1403–1406.

14. Bullen PJ, Rankin JM, Robson SC. Investigation of the epidemiology and prenatal diagnosis of holoprosencephaly in the North of England. *Am J Obstet Gynecol* 2001; **184**: 1256–1262.

15. Matsunaga E, Shiota K. Holoprosencephaly in human embryos: epidemiologic studies of 150 cases. *Teratology* 1977; **16**: 261–267.

16. Dubourg C, Bendavid C, Pasquier L, Henry C, Odent S, David V. Holoprosencephaly. *Orphanet J Rare Dis* 2007; **2**: 8.

17. Hahn JS, Plawner LL. Evaluation and management of children with holoprosencephaly. *Pediatr Neurol* 2004; **31**: 79–88.

18. Baty BJ, Blackburn BL, Carey JC. Natural history of trisomy 18 and trisomy 13: I. Growth, physical assessment, medical histories, survival, and recurrence risk. *Am J Med Genet* 1994; **49**: 175–188.

19. Gilpin SA, Gosling JA. Smooth muscle in the wall of the developing human urinary bladder and urethra. *J Anat* 1983; **137**: 503–512.