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Fetal exomphalos and chromosomal defects: relationship to maternal age and gestation

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ABSTRACT

In an ultrasound screening study involving 15 726 viable, singleton pregnancies at 11–14 weeks of gestation, exomphalos was diagnosed in 0.11% of the cases and, in those with exomphalos, the frequency of trisomy 18, trisomy 13 or triploidy was 61%. The corresponding frequencies of exomphalos of fetuses with these chromosomal defects were 22.5%, 9.1% and 12.5%, respectively. The median maternal age of the screened population was 33 (range 15–48) years, which is higher than in all pregnancies in England and Wales. Expected prevalences of trisomy 18, trisomy 13 and triploidy in the total population were derived on the basis of the age distribution of all deliveries in England and Wales and maternal and gestational age-specific risks for these chromosomal defects. From these numbers and the observed frequencies of exomphalos in association with the various chromosomal defects, it was estimated that the prevalence of exomphalos in a population with the maternal age distribution of all deliveries in England and Wales was 7.4 per 10 000 at 12 weeks of gestation, and this decreased to 3.5 at 20 weeks and 2.9 in live births. The estimated frequency of chromosomal defects in fetuses with exomphalos decreased from 39.4% at 12 weeks of gestation to 27.5% at 20 weeks and 14.4% in live births. The prevalence of chromosomal defects in 153 fetuses with exomphalos referred to our center at 16–26 (median 20) weeks of gestation was not significantly different from that predicted in an unselected population. However, the reported frequency of chromosomal defects in a total of 299 neonates with exomphalos (9.3%) was significantly lower than expected in an unselected population. This study demonstrates that the prevalence of a fetal abnormality and the frequency of associated chromosomal defects depends on the maternal age and gestational age distributions of the populations examined.

INTRODUCTION

Exomphalos, found in about one per 3000 births, is a correctable malformation and, when the condition is isolated, the survival rate is more than 90%. However, a high proportion of fetuses with exomphalos have chromosomal defects, most commonly trisomies 18 or 13; the reported frequency in prenatal ultrasonographic studies varies from 10 to 67% (Table 1)[1–19].

The risk for trisomies 18 ad 13 increases with maternal age and, since these trisomies are associated with a high rate of intrauterine lethality, their prevalence decreases with gestational age[20,21]. Consequently, both the prevalence of exomphalos and that of associated chromosomal defects would be expected to increase with maternal age and decrease with advancing gestation. The aim of this study was to test this hypothesis.

PATIENTS AND METHODS

First-trimester screening study

At the Harris Birthright Research Centre for Fetal Medicine there is an ongoing screening study to investigate the association between increased fetal nuchal translucency thickness at 10–14 weeks of gestation and chromosomal defects[22]. Pregnant volunteers are offered transabdominal first-trimester ultrasound examination. Demographic details and ultrasound findings, including viability, number of fetuses, crown–rump length, nuchal translucency thickness and any obvious defects, are entered into a computer database at the time of scanning. All ultrasound examinations are performed transabdominally (5-MHz or 3.75-MHz curvilinear transducer), but when a fetal defect is suspected, transvaginal sonography (6 MHz) is carried out. A computer search was made for singleton, viable pregnancies with a minimum gestation of 11 weeks and 4 days (crown–rump length of 43 mm); this gestation was selected to exclude cases of physiological herniation of bowel into the umbilical cord.

Second-trimester study on referred patients

The Harris Birthright Research Centre for Fetal Medicine is a referral centre for fetal diagnosis and therapy. A computer search was made for patients who were

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Table 1 Reports on the antenatal diagnosis of exomphalos providing data on the frequency of chromosomal defects

Authors	*n*	*GA* (weeks)	*Chromosomal defects*			
			Total (%)	*Trisomy 18*	*Trisomy 13*	*Other*
Nakayama *et al.* (1984)[1]	10	11–37	10	1	—	—
Nicolaides *et al.* (1986)[2]	12	19–25	66	7	—	1
Gilbert and Nicolaides (1987)[3]	35	16–36	54	17	—	2
Sermer *et al.* (1987)[4]	10	15–40	40	2	1	1
Edyoux *et al.* (1989)[5]	46	15–36	26	6	2	4
Hughes *et al.* (1989)[6]	30	12–40	43	4	5	4
Nyberg *et al.* (1989)[7]	26	12–30	38	4	4	2
Benacerraf *et al.* (1990)[8]	22	14–28	18	1	2	1
Holzgreve *et al.* (1990)[9]	10	12–41	50	3	1	1
Rizzo *et al.* (1990)[10]	12	15–38	58	5	2	—
Getachew *et al.* (1991)[11]	22	15–34	23	3	1	1
Rezai *et al.* (1991)[12]	24	12–40	29	5	1	1
Van de Geijn *et al.* (1991)[13]	22	12–38	45	6	1	3
Fogel *et al.* (1991)[14]	37	16–40	14	3	1	1
Van Zalen-Sprock *et al.* (1991)[15]	18	11–38	39	3	—	4
Nicolaides *et al.* (1992)[16]	116	16–39	36	32	7	3
Wilson *et al.* (1992)[17]	13	13–39	23	3	—	—
Morrow *et al.* (1993)[18]	16	14–24	31	3	—	2
Snijders *et al.* (1995)[19]	18	11–14	67	10	1	1
Total	499	11–41	36	118	29	32

GA, gestational age

referred during 1989–94 at 16–26 weeks of gestation for further assessment, because fetal exomphalos was diagnosed in other hospitals.

Postnatal studies

A literature search was made to identify studies reporting the frequency of chromosomal defects in neonates with exomphalos.

Statistical methods

The expected number of cases of trisomy 18, trisomy 13 and triploidy in a given population was calculated by adding the individual maternal and gestational age-related risks for these chromosomal defects[21]. The maternal age distribution of all deliveries in England and Wales in 1992[23] and the expected prevalences of these chromosomal defects at 12 and 20 weeks of gestation and in live births were then used to derive numbers for the total population. The significance of differences between the expected and observed prevalences of chromosomal defects in the first and second trimester studies and in the neonatal studies was examined by the χ^2 test.

RESULTS

First-trimester screening study

Between October 1992 and December 1994, there were 15 726 viable, singleton pregnancies with a minimum crown–rump length of 43 mm. The median maternal age of the screened population was 33 (range 15–48) years, which was higher than in all pregnancies in England and Wales in 1992 (Figure 1). Fetal karyotyping was performed in 2460 cases, because of increased nuchal translucency thickness ($n = 705$), maternal age ≥ 35 years ($n = 1349$) or parental anxiety ($n = 406$). In the 13 266 cases where fetal karyotyping was not performed, there were 6284 live births and 28 neonatal deaths with no dysmorphic features suggestive of trisomy 18, trisomy 13 or triploidy; there were 117 spontaneous abortions or intrauterine deaths; in 6837 cases the pregnancies are continuing.

In the screened population of 15 726 pregnancies, there were 18 cases (0.11%) of exomphalos, including nine with trisomy 18, one with trisomy 13 and one with triploidy (Table 2). The total observed numbers of trisomy 18, trisomy 13 and triploidy were 40, 11 and 8, respectively; these were similar to the numbers expected on the basis of the maternal and gestational age distribution of this population ($n = 33$, $\chi^2 = 0.67$; $n = 10$, $\chi^2 = 0.05$; and $n = 8$, $\chi^2 = 0.00$, respectively)[21]. The prevalence of exomphalos in fetuses with trisomy 18 was 22.5%, in those with trisomy 13 it was 9.1%, in those with triploidy it was 12.5%, and in those with no evidence of these chromosomal defects it was 0.045% (Table 2). In three of the seven (42.9%) chromosomally normal fetuses, there were additional major lethal abnormalities (two cases of body stalk defect and one case of anencephaly).

Expected prevalences in the total population

The expected number of cases with trisomy 18, trisomy 13 and triploidy in 100 000 pregnancies with the maternal age distribution of all deliveries in England and Wales was calculated using estimates of maternal and gestational age-specific risks[21]. For each year of maternal age, the expected prevalence of chromosomal defects on

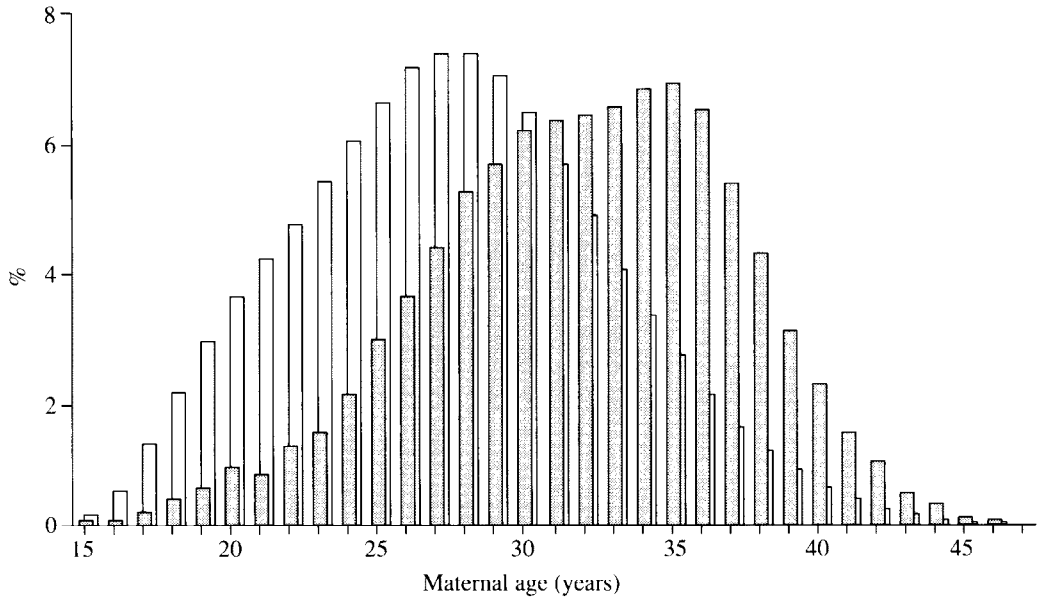

Figure 1 Maternal age distribution of the 15 726 pregnancies in the first-trimester screening study (closed bars) and all deliveries in England and Wales in 1992[23] (open bars)

Table 2 Observed prevalence of trisomy 18, trisomy 13, triploidy and exomphalos at 10–14 weeks of gestation in 15 726 women with a median age of 33 years. In the last column is the percentage of fetuses with exomphalos in each karyotype group

Karyotype	*n*	*Exomphalos*	*Exomphalos* (%)
Trisomy 18	40	9	22.500
Trisomy 13	11	1	9.091
Triploidy	8	1	12.500
Other	15 667	7	0.045
Total	15 726	18	0.114

the basis of the mean gestation at examination was multiplied by the number of women in the age group. The sum of numbers for each year of maternal age provided the expected total for the whole group (Table 3). The prevalence of triploidy is not related to maternal age; the expected numbers for triploidy was derived assuming prevalences of 0.03% at 12 weeks, 0.0004% at 20 weeks and less than 0.00001% in live births, respectively[21].

To derive the number of cases with exomphalos in each karyotype group (Table 4), the expected number of cases (Table 3) was multiplied by the observed frequencies of exomphalos in the screening study at 11–14 weeks of gestation (Table 2). In the group with no evidence of trisomy 18, trisomy 13 or triploidy, the prevalence of exomphalos at 11–14 weeks was assumed to be 0.045% and at 20 weeks and in live births it was assumed to be 0.025% (derived on the assumption that fetuses with lethal additional abnormalities, such as anencephaly, would have died before 20 weeks of gestation). Therefore, in an unselected population of 100 000 deliveries with the maternal age distribution of all pregnancies in England and Wales, the expected number of fetuses with exomphalos at 12 weeks of gestation is 74, at 20 weeks it is 35 and in live births it is 29 (Table 4).

Second-trimester study on referred patients

In the 153 pregnancies with exomphalos at 16–26 weeks of gestation, the median maternal age was 29 (range 16–48) years and fetal karyotyping demonstrated 34 (22.2%) cases with trisomy 18, eight (5.2%) with trisomy 13 and one (0.7%) with triploidy. The prevalence of chromosomal defects was relatively high in those where the sac contained bowel only (32/70 or 46%) compared to the prevalence in the group where it contained other organs (16/83 or 19%).

In an unselected population of 100 000 pregnancies with the maternal age distribution of all deliveries in England and Wales, the total expected number of fetuses with exomphalos at 20 weeks of gestation is about 35, and the estimated frequency of trisomy 18, trisomy 13 and triploidy in these 35 fetuses is 23.4%, 3.5% and 0.6%, respectively (Table 5). Therefore, the observed frequencies of trisomies and triploidy in the referred population were similar to those expected in an unselected population (Table 5).

Reported prevalence in postnatal studies

In six studies on neonates with exomphalos, the mean frequency of trisomies 18 or 13 was 9.3% (Table 6)[24–29], which was significantly lower than the 14.4% expected for an unselected population (Table 7). Thus, as shown in Table 4, in an unselected population of 100 000 live births, the total expected number of babies with exomphalos is about 29; the estimated frequency of trisomies 18 and 13 in these 29 fetuses is 12.8% and 1.7%, respectively.

Table 3 Estimates for the number of fetuses with trisomy 18 or trisomy 13 at different stages of pregnancy in 100 000 pregnancies. The total number of cases in each age bracket (*n*) was derived from the distribution of maternal age for all deliveries in England and Wales in 1992[23]

Maternal age (years)	*n*	*Trisomy 18*			*Trisomy 13*		
		12 weeks	*20 weeks*	*Birth*	*12 weeks*	*20 weeks*	*Birth*
< 25	30 800	12.1	4.9	2.7	3.9	1.8	0.8
25–29	35 534	18.3	7.5	3.2	5.9	2.8	1.2
30–34	24 102	23.0	9.3	4.1	7.4	3.5	1.5
35–39	8 132	22.1	8.9	3.9	7.1	3.4	1.5
40–44	1 373	12.7	5.2	2.2	4.1	1.9	0.8
≥ 45	59	1.8	0.7	0.3	0.6	0.3	0.1
Total	100 000	90.0	36.5	16.4	29.0	13.7	5.9

Table 4 Expected prevalences of trisomy 18, trisomy 13, triploidy and exomphalos in each karyotypic group at 12 and 20 weeks of gestation and in live births in a population with the maternal age distribution of all deliveries in England and Wales in 1992[23]

	12 weeks		*20 weeks*		*Live births*	
Karyotype	*n*	*Exomphalos*	*n*	*Exomphalos*	*n*	*Exomphalos*
Trisomy 18	90	20.3	36.5	8.1	16.4	3.7
Trisomy 13	29	2.6	13.7	1.2	5.9	0.5
Triploidy	50	6.3	1.4	0.2	0.0	0.0
Other	99 831	45.0	99 949	25.0	99 978	25.0
Total	100 000	74.2	100 000	34.5	100 000	29.2

Table 5 Observed frequency of trisomy 18, trisomy 13 and triploidy in 153 fetuses with exomphalos at 16–26 weeks of gestation and expected frequencies at 20 weeks of gestation in an unselected population with the maternal age distribution of all deliveries in England and Wales[23]. There were no significant differences between observed and expected frequencies

Karyotype	*Observed* (%)	*Expected* (%)	χ^2
Trisomy 18	22.2	23.4	0.07
Trisomy 13	5.2	3.5	0.53
Triploidy	0.7	0.6	0.00
Total	28.1	27.5	0.01

Table 6 Studies reporting the frequency of chromosomal defects in neonates with exomphalos

Authors	*n*	*Trisomy 18*	*Trisomy 13*
Carpenter *et al.* (1983)[24]	25	0 (0%)	1 (4%)
Kirk and Wah (1983)[25]	38	2 (5%)	1 (3%)
Wladimiroff *et al.* (1983)[26]	46	3 (7%)	2 (4%)
Mabogunje and Mahour (1984)[27]	57	3 (5%)	2 (4%)
Hasan and Hermansen (1986)[28]	17	1 (6%)	1 (6%)
Calzolari *et al.* (1993)[29]	116	6 (5%)	6 (5%)
Total	299	15 (5.0%)	13 (4.3%)

Table 7 Observed frequency of trisomy 18, trisomy 13 and triploidy in 299 neonates with exomphalos and expected frequencies in live births in an unselected population with the maternal age distribution of all deliveries in England and Wales[23]. The observed frequency was significantly lower than the expected

Karyotype	*Observed* (%)	*Expected* (%)	χ^2
Trisomy 18	5.0	12.7	11.2*
Trisomy 13	4.3	1.7	3.16
Triploidy	0.0	0.0	—
Total	9.3	14.4	4.02*

*$p < 0.05$

DISCUSSION

The data of this study demonstrate that the prevalence of exomphalos and that of associated chromosomal defects are much higher at 11–14 weeks of gestation than in the second trimester of pregnancy or in live births. Thus, the estimated prevalence of exomphalos in a population with the maternal age distribution of all deliveries in England and Wales, which is very similar to that of the USA[30], is 7.4 per 10 000 at 12 weeks of gestation, and this decreases to 3.5 at 20 weeks and 2.9 in live births. Similarly, the estimated frequency of chromosomal defects in fetuses with exomphalos decreases from 39.4% (29.2 of 74.2) at 12 weeks of gestation to 27.5% (9.5 of 34.5) at 20 weeks and 14.4% (4.2 of 29.2) in live births (Table 4). These findings are not surprising, since exomphalos is a common feature of chromosomal defects that are associated with a high rate of intrauterine lethality.

Ultrasound studies examining the association between fetal abnormalities and chromosomal defects often fail to take into account the maternal age and gestational age distribution of their population and inevitably report a wide range of results; the reported frequency of chromosomal defects in fetuses with exomphalos varies from 10 to 66% (Table 1)[1–19].

In the second-trimester study, the frequency of chromosomal defects in our fetuses with exomphalos (28.1%) was similar to that expected on the basis of the maternal age and gestational age distribution of an unselected population (27.5%). These data suggest that the patients with exomphalos examined in a referral center are representative of an unselected population of fetuses with this abnormality. These findings are likely to be the consequence of (1) easy diagnosis of all or most cases of exomphalos at routine ultrasound examination; and (2) the fact that all or most cases of exomphalos are referred for fetal karyotyping. For example, if only fetuses with the most severe types of exomphalos were diagnosed, then the observed frequency of chromosomal defects would have been lower than expected, because the incidence of chromosomal defects is higher in those cases where the exomphalos sac contains only bowel rather than liver and other organs[7,11,16]. Similarly, if in the routine centers there was patient preselection, so that fetuses with multiple additional abnormalities were more likely to be referred for fetal karyotyping rather than those with isolated exomphalos, then the observed frequency of chromosomal defects in reports from referral centers would have been higher than expected.

In the postnatal studies, the reported frequency of chromosomal defects in neonates with exomphalos (9.3%)[24–29] was lower than expected on the basis of the maternal age and gestational age distribution of an unselected population (14.4%). One explanation for this finding is that ever since the introduction of ultrasound many cases of exomphalos and aneuploidy have been identified antenatally and parents have opted for termination of such pregnancies. In addition, the birth prevalence may be underestimated when based on series from neonatal surgical units, since babies with obvious features of lethal chromosomal abnormalities may not always be referred for intervention.

This study demonstrates a methodology for the assessment of studies reporting on the association between fetal abnormalities and chromosomal defects. It shows the need to take into account the maternal age and gestational age distributions of the populations examined.

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