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FETAL CHOROID PLEXUS CYSTS AND TRISOMY 18: ASSESSMENT OF RISK BASED ON ULTRASOUND FINDINGS AND MATERNAL AGE

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SUMMARY

This paper examines the association between fetal choroid plexus cysts (CPCs) and trisomy 18 and proposes a method by which risks can be derived taking into account both sonographic findings and maternal age. Data from our centre on the sonographic findings of 58 fetuses with trisomy 18 and 387 fetuses with CPCs as well as data from published series were used. It was calculated that the prevalence of CPCs in the general population is approximately 1 per cent and at mid-gestation the incidence of CPCs in fetuses with trisomy 18 is approximately 50 per cent. In the 387 fetuses with CPCs, the incidence of trisomy 18 increased with maternal age and the likelihood ratio for trisomy 18 increased with the number of additional abnormalities, from 0·03 for those with isolated CPCs to 0·4 if there was one additional abnormality and 20·5 if there were two or more additional abnormalities. It was concluded that if the cysts are apparently isolated, the risk for trisomy 18 is only marginally increased and maternal age should be the main factor in deciding whether or not to offer fetal karyotyping. If one additional abnormality is found, the maternal age-related risk is increased, so that even for a 20-year-old the risk for trisomy 18 is at least as high as the risk for trisomy 21 in a 35-year-old. In this respect, it may be considered desirable to offer such patients the option of karyotyping.

KEY WORDS—Fetal choroid plexus cysts, fetal karyotype, trisomy 18, maternal age.

INTRODUCTION

Major chromosomal defects are associated with fetal abnormalities that are amenable to prenatal diagnosis by ultrasound. Indeed, several reports have established that in fetuses with sonographically detectable malformations, such as choroid plexus cysts (CPCs), the frequency of chromosomal abnormalities is much higher than the cut-off point used routinely for offering fetal karyotyping on the basis of maternal age or maternal serum biochemistry (Nicolaides *et al.*, 1993). For example, in a study of 2086 fetuses that were karyotyped because of fetal abnormalities and/or intrauterine growth retardation, 301 (14 per cent) were chromosomally abnormal (Nicolaides *et al.*, 1992). However, the majority of chromosomally abnormal fetuses have multiple defects. For apparently isolated defects, there are large differences in the reported incidence of associated chromosomal abnormalities (Table I) and it is uncertain whether in such cases karyotyping should be undertaken, especially for those defects, such as CPCs, that have a high prevalence in the general population. Since the incidence of chromosomal abnormalities is associated with maternal age, it is possible that the contradictory results of the various studies are the mere consequence of differences in maternal age distribution of the populations examined.

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Table I—Summary of reports on the prenatal diagnosis of choroid plexus cysts providing data on maternal age, gestational age (GA), diameter of the cysts, and incidence of chromosomal abnormalities. Studies are classified as CPCs when only findings in fetuses with choroid plexus cysts were included, high risk if they were on referred populations and those referred because of choroid plexus cysts were included, 'routine' if they were on referred populations but those referred because of choroid plexus cysts were excluded, and routine if they were unselected population-based studies. Results on abnormal karyotype are divided according to whether the choroid plexus cysts were isolated or there were additional sonographic abnormalities

				Fetal choroid plexus cysts (CPCs)						
						Incidence of chromosomal defects				
Reference	Maternal age (years)	GA (weeks)	*n*	*n*	Size (mm)	%	Isolated CPCs	Multiple abnormalities	Trisomy 18	Other*
CPCs										
Nicolaides *et al.* (1986)	?	16–39	?	4	Large	75	—	3/4	3	—
Rickets *et al.* (1987)	?	19–23	?	4	4–10	25	—/3	1/1	—	1
Benacerraf and Laboda (1989)	?	18–28	?	38	?	0	—/38	—	—	—
Thorpe-Beeston *et al.* (1990)	?	15–37	?	83	3–21	24	—/49	20/34	17	3
Nadel *et al.* (1992)	?	14–27	?	234	?	5	—/220	12/14	11	1
High risk										
Gabrielli *et al.* (1989)	?	16–28	933	82	?	5	—/75	4/7	4	—
Zerres *et al.* (1991)	?	?	823	25	?	20	—/14	5/11	4	1
'*Routine*'										
Chitkara *et al.* (1988)	?	16–42	6288	41	3–20	2	—/38	1/3	1	—
Clark *et al.* (1988)	?	16–22	2820	5	3–14	0	—/5	—	—	—
DeRoo *et al.* (1988)	30 (19–40)	14–21	2084	17	>2	0	—/17	—	—	—
Chan *et al.* (1989)	79%>35	15–24	513	13	3–10	0	—/13	—	—	—
Platt *et al.* (1991)	?	15–22	7350	71	?	6	—/67	4/4	3	1
Perpignano *et al.* (1992)	?	14–33	3769	87	⩾2	7	5/86†	1/1	4	2
Porto *et al.* (1993)	33 (16–47)	15–22	3247	63	2–12	10	2/59‡	4/4	3	3
Routine										
Ostlere *et al.* (1990)	?	16–18	11 700	100	⩾2	3	—/96	3/4	3	—
Achiron *et al.* (1991)	25 (18–40)	18–22	5400	30	?	7	1/29	1/1	2	—
Chinn *et al.* (1991)	30 (19–41)	18–24	1045	38	⩾2	3	—/36	—/2	—	—
Twinning *et al.* (1991)	?	18–20	4541	19	⩾3	11	—/16	2/3	2	—
Howard *et al.* (1992)	?	18–20	4765	51	?	2	1/51	—	1	—

*Trisomy 21, n=46,XY, − 14t(14;21), n=3; triploidy, n=3; mosaic Turner syndrome, n=1.
†Trisomy 18, n=3; trisomy 21, n=1; mosaic Turner syndrome, n=1.
‡Trisomy 21, n=1; 47,XXY, n=1.

The aim of this study is to propose a model for the calculation of risks for chromosomal abnormalities based on ultrasonographically detectable fetal abnormalities and maternal age. The example of CPCs and their relation to trisomy 18 was selected because CPCs are potentially good markers in as much as they are easily seen in the standard section of the fetal head used routinely for measurement of the biparietal diameter. Furthermore, during the last 8 years several prenatal studies have been performed and the accumulated data make it possible to draw some conclusions as to the possible association between CPCs and trisomy 18. In addition, since CPCs are common, a recommendation in favour of invasive testing would have major implications in terms of both health-care resources and fetal death.

PATIENTS AND METHODS

In trying to develop a model for the calculation of risks for trisomy 18 in mid-trimester fetuses with CPCs, it was essential to establish (1) the prevalence of trisomy 18 at mid-gestation, (2) the prevalence of CPCs at mid-gestation, (3) the prevalence of CPCs in fetuses with trisomy 18, and (4) the incidence of additional abnormalities in fetuses with CPCs. Information on (1) and (2) was obtained from a review of the literature. For (3) and (4), data collected in our centre were used.

Patients were selected retrospectively from our database, which contained findings from 17 583 pregnancies seen between January 1987 and March 1993, if either fetal CPCs or trisomy 18 was diagnosed at 16–23 weeks' gestation. In all cases, a detailed ultrasound examination was performed and all findings were recorded at the time of scanning. The diagnosis of fetal malformations was based on the demonstration of anatomical defects (Nicolaides *et al.*, 1992) and/or abnormal fetal biometry (Snijders *et al.*, 1994).

In pregnancies with CPCs, our policy was to offer the parents the option of karyotyping. It was explained that in the presence of additional malformations the risk was thought to be high, whereas if the cysts were isolated the risk was uncertain but perhaps similar to the risk of fetal loss from invasive testing (approximately 0·5–1·0 per cent).

RESULTS

Prevalence of trisomy 18 at mid-gestation

Estimates of maternal age-specific risks for trisomy 18 at mid-gestation were derived from the incidences of trisomies 21 and 18 at mid-trimester amniocentesis for maternal age (Ferguson-Smith and Yates, 1984; Hook *et al.*, 1988) and from the maternal age-specific incidence of trisomy 21 in livebirths (Cuckle *et al.*, 1987). In women aged 35–45 years, the observed incidence of trisomy 21 at mid-gestation was 1·5 times higher than expected on the basis of incidences in livebirths, and the relative frequency of trisomy 18 compared with trisomy 21 was 0·2. Therefore, to derive estimates of the mid-trimester incidence of trisomy 18 for women of all ages, incidences of trisomy 21 in livebirths were multiplied by $1{\cdot}5 \times 0{\cdot}2$ (Snijders *et al.*, 1994).

Prevalence of choroid plexus cysts at mid-gestation

Five of the studies in Table I provided data from routine scanning of the whole population at 16–24 weeks and the prevalence of CPCs was 238 of 27 451 or 0·87 per cent (Ostlere *et al.*, 1990; Achiron *et al.*, 1991; Chinn *et al.*, 1991; Twinning *et al.*, 1991; Howard *et al.*, 1992). In addition, there were seven papers that reported findings in referred populations but excluded referrals for CPCs (Chitkara *et al.*, 1988; Clark *et al.*, 1988; DeRoo *et al.*, 1988; Chan *et al.*, 1989; Platt *et al.*, 1991; Perpignano *et al.*, 1992); when data from these studies were included, the prevalence of CPCs was 1·00 per cent (535 of 53 522).

Prevalence of choroid plexus cysts in trisomy 18

In our group of 58 fetuses with trisomy 18, CPCs of ≥ 3 mm in diameter were diagnosed in 38 (66 per cent). In two previous studies, the incidences of CPCs in fetuses with trisomy 18 at 15–24 weeks' gestation were 29 per cent (5 of 17; Benacerraf *et al.*, 1990) and 37 per cent (10 of 27; Nyberg *et al.*, 1993).

Additional abnormalities in fetuses with CPCs

In our group of 387 fetuses with CPCs, karyotyping was performed in 213 cases. In the 107 with isolated CPCs, there were two chromosomal defects (one trisomy 18 and one trisomy 21); in the 106 with additional abnormalities, there were 43

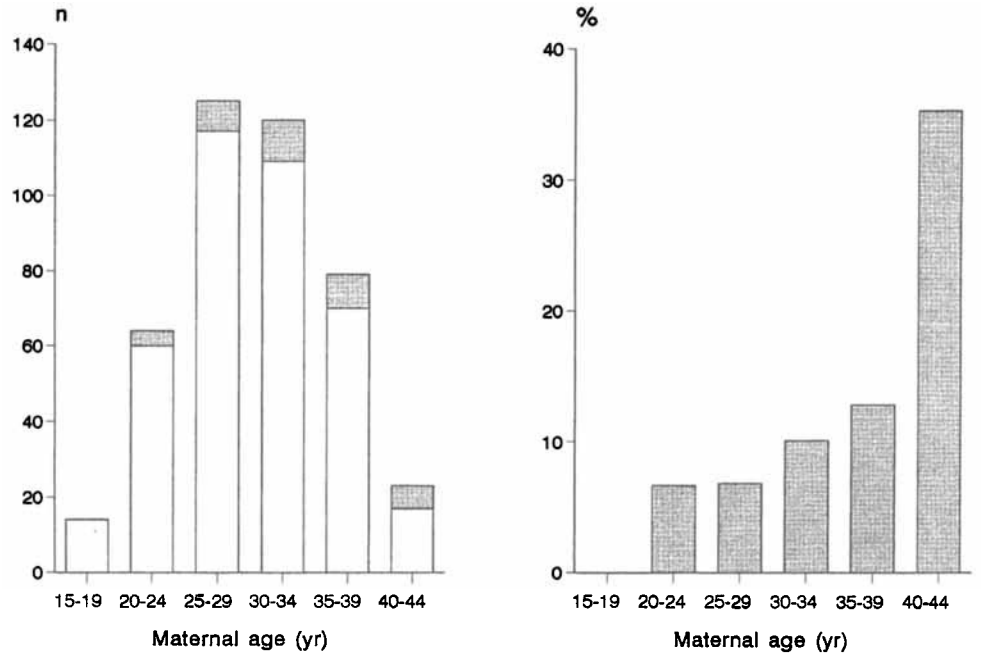

Fig. 1—Maternal age distribution (left) and the incidence of trisomy 18 in relation to maternal age (right) in fetuses with CPCs

chromosomal defects (37 trisomies 18, three trisomies 21, one partial trisomy 21q, one trisomy 13, and one deletion of chromosome 13). In the group of 174 fetuses with CPCs where no karyotyping was performed, there were 164 cases resulting in livebirths and none of the infants had any features of chromosomal abnormalities. In two cases, the pregnancies were terminated because of spina bifida and cystic adenomatoid malformation, respectively, and in two cases, there were unexplained stillbirths (at post-mortem examination none of these four fetuses had any features suggestive of trisomy 18). In an additional six cases, no follow-up could be obtained because the patients had changed address and hospital.

From the total group of 387 fetuses with CPCs, 332 were considered to be chromosomally normal (the 168 cases that were proven to be chromosomally normal and the 164 cases resulting in normal infants with no features of chromosomal abnormalities). The types and number of additional abnormalities in these 332 fetuses are summarized in Table II. Additional abnormalities were found in 61 cases (18 per cent). If only morphological abnormalities were considered, the incidence of additional abnormalities was 4 per cent (14 cases).

The sonographically detectable abnormalities in the 38 fetuses with trisomy 18 and CPCs are shown in Table II; in 97 per cent, there were additional morphological and/or biometrical abnormalities. If only morphological abnormalities were considered, the incidence of multiple abnormalities was 92 per cent. In the screening studies in Table I, there were 19 fetuses with CPCs and trisomy 18; in 14 (74 per cent) there were additional abnormalities, but in five (26 per cent) CPCs were apparently the only defect.

Incidence of trisomy 18 in relation to maternal age and the number of additional abnormalities in fetuses with CPCs

In the group of fetuses with CPCs, the incidence of trisomy 18 was significantly associated with maternal age (Fig. 1; $r=0{\cdot}87$, $P<0{\cdot}0001$). For each fetus with CPCs (chromsomally normal and abnormal), the total number of defects was counted. The incidence of trisomy 18 increased with the number of defects (Fig. 2; $r=0{\cdot}88$, $P<0{\cdot}0001$). Table III shows the likelihood ratios for trisomy 18 in fetuses with CPCs in relation to the number of additional defects. For fetuses with isolated CPCs the ratio is 0·03; for fetuses with

Table II—Incidence of additional defects in 332 fetuses with an apparently normal karyotype and 38 fetuses with trisomy 18 where choroid plexus cysts were diagnosed at 16–23 weeks' gestation

	Normal	Other defects		Trisomy 18	Other defects				
		1	2		1	2	3	4	⩾5
	(*n*=332)	(*n*=46)	(*n*=15)	(*n*=38)	(*n*=2)	(*n*=6)	(*n*=2)	(*n*=8)	(*n*=19)
Anatomical									
Clenched hand	1 (0·3%)	—	1	24 (63%)	—	4	—	5	15
Strawberry shaped head	1 (0·3%)	—	1	24 (63%)	—	1	2	3	18
Heart defects	1 (0·3%)	—	1	17 (45%)	—	3	—	2	12
Micrognathia	1 (0·3%)	—	1	15 (39%)	—	—	—	1	14
Exomphalos	1 (0·3%)	—	1	11 (29%)	—	1	1	1	8
Talipes equinovarus	3 (0·9%)	1	2	8 (21%)	—	—	—	1	7
Facial cleft	0 (0·0%)	—	—	5 (13%)	—	—	—	3	2
Rocker-bottom feet	0 (0·0%)	—	—	5 (13%)	—	—	—	—	5
Nuchal oedema	4 (1·2%)	2	2	4 (11%)	—	1	—	2	1
Multicystic kidneys	3 (0·9%)	1	2	4 (11%)	—	1	—	2	1
Severe hydronephrosis	2 (0·6%)	1	1	0 (0%)	—	—	—	—	—
Absent stomach bubble	0 (0·0%)	—	—	4 (11%)	—	—	—	—	4
Diaphragmatic hernia	0 (0·0%)	—	—	3 (8%)	—	—	—	1	2
Hydrops fetalis	0 (0·0%)	—	—	2 (3%)	—	—	—	1	1
Posterior fossa cyst	0 (0·0%)	—	—	2 (3%)	—	—	—	1	1
Absent corpus callosum	0 (0·0%)	—	—	1 (2%)	—	—	—	—	1
Cystic adenomatoid malformation	0 (0·0%)	—	—	1 (2%)	—	—	—	—	1
Spina bifida	0 (0·0%)	—	—	1 (2%)	—	—	—	—	1
Kyphoscoliosis	2 (0·6%)	1	1	0 (0%)	—	—	—	—	—
Biometrical									
Small for gestational age	8 (2·4%)	4	4	17 (45%)	—	—	—	5	12
Brachycephaly	8 (2·4%)	5	3	13 (34%)	2	—	2	1	8
Short femur	7 (2·1%)	3	4	9 (24%)	—	—	1	2	6
Pyelectasia	26 (7·8%)	21	5	10 (26%)	—	—	—	—	10
Ventriculomegaly	9 (2·7%)	7	2	5 (13%)	—	—	—	1	4
Microcephaly	2 (0·6%)	—	2	2 (5%)	—	1	—	—	1

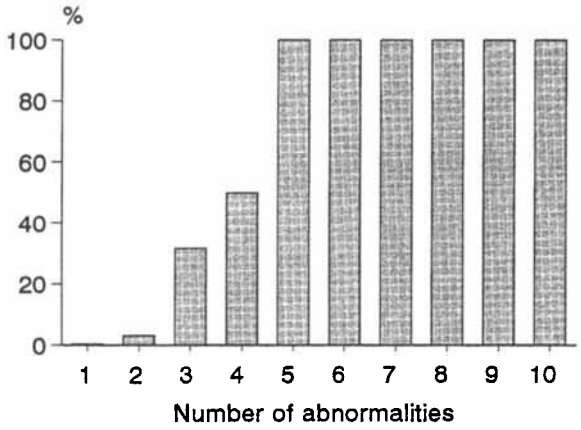

Fig. 2—Relationship between the incidence of trisomy 18 in fetuses with choroid plexus cysts and the number of ultrasonographically detectable abnormalities

CPCs and one additional abnormality the ratio is 0·4; and for fetuses with CPCs and two or more additional abnormalities the ratio is 20·5.

Calculation of risks on the basis of ultrasound findings and maternal age

In the calculation of risks for trisomy 18 in mid-trimester fetuses with CPCs, the following assumptions were made: (1) the risk for trisomy 18 increases with advancing maternal age; (2) the prevalence of CPCs in the general population is approximately 1 per cent; (3) at mid-gestation the incidence of CPCs in fetuses with trisomy 18 is approximately 50 per cent; and (4) within the group of fetuses with CPCs, the likelihood ratio for trisomy 18 increases with the number of additional abnormalities.

The estimated maternal age-related risks for trisomy 18 in the presence of fetal CPCs and additional abnormalities are shown in Table IV. To illustrate how the calculations were made, the example of a 22-year-old woman was used. The maternal age-related risk for trisomy 18 at mid-gestation is approximately 1/4500 (Snijders *et al.*, 1994). Since CPCs are present in 50 per cent of fetuses with trisomy 18, if no CPCs are found the risk is 0·5/4500 or 1/9000. Since 1 per cent of all fetuses have CPCs and 50 per cent of fetuses with trisomy 18 have CPCs, the incidence of trisomy 18 in the presence of fetal CPCs is 0·50/(4500 × 0·01) or 1/90.

To derive risks for fetuses with and without additional abnormalities, overall risks for fetuses with CPCs were expressed as odds ratios (the number of abnormal pregnancies to the number of normal pregnancies) and the left-hand side of the odds ratio was multiplied by the appropriate likelihood ratio. Therefore, for the 22-year-old woman, when the CPCs are isolated, the risk is approximately 1/2950; when there is one additional defect, the risk is 1/225; and when there are two or more additional defects, the risk is 1/5.

DISCUSSION

Ultrasonographic examination can identify anatomical or biometrical defects that are commonly found in chromosomally abnormal fetuses. However, the majority of fetuses with a given defect are chromosomally normal. This study illustrates the steps necessary to derive risks taking into account maternal age and the presence or absence of additional defects.

CPCs are useful markers for fetal trisomy 18 because they are present in 30–70 per cent of affected fetuses and they are easily seen in the standard biparietal diameter view which is obtained for all routine ultrasound scans. The detection of fetal CPCs should stimulate the sonographer to search for additional abnormalities. If the cysts are apparently isolated, the risk for trisomy 18 is only marginally increased and maternal age should be the main factor in deciding whether or not to offer fetal karyotyping. If one additional abnormality is found, the maternal age-related risk is increased by abut 20 times, so that even for a 22-year-old the risk for trisomy 18 (1/225) is similar to the risk for trisomy 21 in a 35-year-old (1/258); in this respect, it may be considered rational to offer such patients the option of karyotyping. If two or more additional abnormalities are found, the risk is increased by almost 1000 times and karyotyping should be offered irrespective of maternal age.

In our calculations it was assumed that the prevalence of CPCs at 16–24 weeks' gestation is 1 per cent. In those studies that diagnosed CPCs with a minimum diameter of 2 mm rather than 3 mm, the prevalence tended to be higher (Table I). In addition, the prevalence for the 2 mm CPCs was higher in the more recent studies, presumably reflecting improved resolution in ultrasound equipment. However, in all cases of trisomy 18 the diameter of the CPCs was $\geqslant 3$ mm. In two studies, the upper gestational age of the fetuses was >24

Table III—Number of additional defects in 370 fetuses with choroid plexus cysts in the presence of trisomy 18 (n=38) or an apparently normal karyotype (n=332). The likelihood ratio is the ratio of the frequency with which 0, 1, and ⩾2 additional defects were observed in the group with trisomy 18 to the respective frequencies in the chromosomally normal group

No. of additional defects	Trisomy 18 (n=38)	Normals (n=332)	Likelihood ratio
0	1 (2·6%)	271 (81·6%)	0·03
1	2 (5·3%)	46 (13·9%)	0·4
⩾2	35 (92·1%)	15 (4·5%)	20·5

Table IV—Estimates of the risk for trisomy 18 in fetuses with and without choroid plexus cysts (CPCs) and one or more additional defects

Maternal age (years)	Overall	CPCs absent	CPCs present			
			Overall	Isolated	+1 defect	+>1 defects
20–24	1/4500	1/9000	1/90	1/2950	1/225	1/5
25–29	1/3600	1/7200	1/70	1/2300	1/175	1/4
30–34	1/2000	1/4000	1/40	1/1300	1/100	1/3
35–39	1/750	1/1500	1/15	1/470	1/35	<1/2
40–44	1/200	1/400	1/4	1/100	1/10	<1/2

weeks and the prevalence would have been underestimated because CPCs usually resolve after this gestation.

The prevalence of choroid plexus cysts in trisomy 18 was assumed to be 50 per cent. This was derived from combining our data (66 per cent) with those of two previous studies (29 and 37 per cent, respectively). The large differences between the studies may be the consequence of, firstly, the relatively small number of cases in each study; secondly, differences in the referred populations; and thirdly, under-diagnosis of CPCs in the studies of Benacerraf *et al.* (1990) and Nyberg *et al.* (1993) which included cases from the early 1980s. Prenatal diagnosis of CPCs was first reported in 1984 (Chudleigh *et al.*, 1984) and it was not until 1986 that the possibility of an association with trisomy 18 was raised (Nicolaides *et al.*, 1986).

The incidence of additional abnormalities in our 38 fetuses with trisomy 18 (97 per cent) was higher than that in the combined group of 19 fetuses from previous studies (74 per cent). One possible explanation for this difference is that we had much experience on the sonographic expression of trisomy 18 (108 cases during the last 10 years), and since our first suspicion on the association between CPCs and trisomy 18 (Nicolaides *et al.*, 1986), in all cases of CPCs we have undertaken a systematic search for possible anatomical and biometrical abnormalities. This is also true for other referral centres; for example, Benacerraf *et al.* (1990) reported that in 1983–1989 they found additional abnormalities in four or five fetuses with CPCs and trisomy 18 at 15–19 weeks, whereas in 1988–1992 the same group found additional defects in all 11 cases (Nadel *et al.*, 1992).

In 18 per cent of chromosomally normal fetuses with CPCs we found additional abnormalities, which is much higher than the 4 per cent from previous studies (Table II). However, in these studies no details were provided as to which abnormalities were systematically searched for. If biometrical abnormalities were considered, the incidence should have been higher; by definition, for each parameter 5 per cent of the normal population will have values outside the 95 per cent confidence interval of the normal range. In our group, if biometrical abnormalities were excluded

the incidence of additional defects would also be 4 per cent.

Practising sonographers receive contradictory advice from published studies as to whether karyotyping should be offered for apparently isolated CPCs. This paper offers risk tables that provide at least some guidelines for counselling parents. The paper also raises the questions that need to be answered by future studies to validate each parameter used for the derivation of risk tables, not only for CPCs and trisomy 18, but also for other sonographic markers of chromosomal abnormalities.

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