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Fetal Renal Defects: Associated Malformations and Chromosomal Defects

Abstract

During a 6-year period (1985–1990) blood karyotyping was performed in 682 fetuses with renal defects. There were: 276 fetuses with mild hydronephrosis; 206 with moderate/severe hydronephrosis; 173 with multicystic dysplasia, and 27 with renal agenesis. The overall incidence of chromosomal abnormalities was 12% (trisomies, n = 63; deletions, n = 9; triploidies, n = 5, and sex chromosome aneuploidies, n = 8). There were more than twice as many males than females, but the incidence of chromosomal defects in females was almost double (18%) than in males (10%). Furthermore, compared to the overall maternal age-related risk, the risk for fetal chromosomal abnormalities was three times higher when there was an isolated renal defect and thirty times higher when there were additional malformations. The risk of chromosomal abnormalities was similar for fetuses with unilateral or bilateral involvement, different types of renal defects, urethral or ureteric obstruction, and oligohydramnios or normal/reduced amniotic fluid volume. Nevertheless, the patterns of chromosomal abnormalities, and consequently that of associated malformations, were related to the different types of renal defects.

Key Words
Renal defects, fetal
Prenatal diagnosis
Ultrasonography
Karyotype, fetal
Cordocentesis

Introduction

Postnatal and postmortem studies have established that urinary tract defects are commonly found in many chromosomal abnormalities [1]. Data on antenatally diagnosed renal defects are derived from a small number of often unclassified 'renal defects' and the reported incidence of associated chromosomal abnormalities varies from 2 to 33% (table 1) [2–13].

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Table 1. Summary of reports on antenatally diagnosed renal anomalies with data on presence of other defects and their karyotype

Author study	Renal defects	Abnormal karyotype			Trisomies			Other[1]
		total	isolated	other	13	18	21	
Curry et al., 1984 [2] Postmortem[2]	mixture	3/41	0/30	3/11	–	–	1	2
Nicolaides et al., 1986 [3] Prenatal U/S	mixture	11/45	–	–	2	6	–	3
Rizzo et al., 1987 [4] Prenatal U/S	multicystic dysplasia	2/6	0/3	2/3	1	–	–	1
Boue et al., 1988 [5] Prenatal U/S	mixture	24/221	10/165	14/56	3	6	5	10
Hegge et al., 1988 [6] Prenatal U/S	mixture	1/3	–	–	–	–	–	1
Reuss et al., 1988 [7] Prenatal U/S	obstructive uropathy	5/43	2/27	3/16	2	2	1	–
Eydoux et al., 1989 [8] Prenatal U/S	mixture	12/111	1/55	11/56	3	4	2	3
Benacerraf et al., 1990 [9] Prenatal U/S	mild hydronephrosis	7/210	–	–	–	–	7	–
Holzgreve et al., 1990 [10] Prenatal U/S	mixture	4/16	–	–	2	1	–	1
Rizzo et al., 1990 [11] Prenatal U/S	mixture	1/44	1/44	–	–	–	–	1
Shah et al., 1990 [12] Prenatal U/S	mixture	3/9	–	–	1	–	1	1
Stoll et al., 1990 [13] Prenatal[3]	mixture	21/79	–	–	4	6	4	7
Total, %		11	4	23	19	27	22	32

[1] 46,XY,der(18),t(5;18)(p15,q21), 46,XY(4p–), 46,XX,del(18)(q22;qter), 69XXY, 46,XYdel(2q), 45X0, 46,XX,del(4)(p15), Ring chromosome 22, 47,XX,(10p+), 46,XX/47,XX,i(5p+), 47,XX,(4q+), 46,XX,–3+der(3),t3; 11(p25,q13.2), 46,XX,6qt, 46,XX/47,XX,9p+, others.

[2] Postmortem study including 8 cases that were diagnosed antenatally.

[3] 54.4% diagnosed antenatally; the others stillborn or liveborn up to age 5 years.

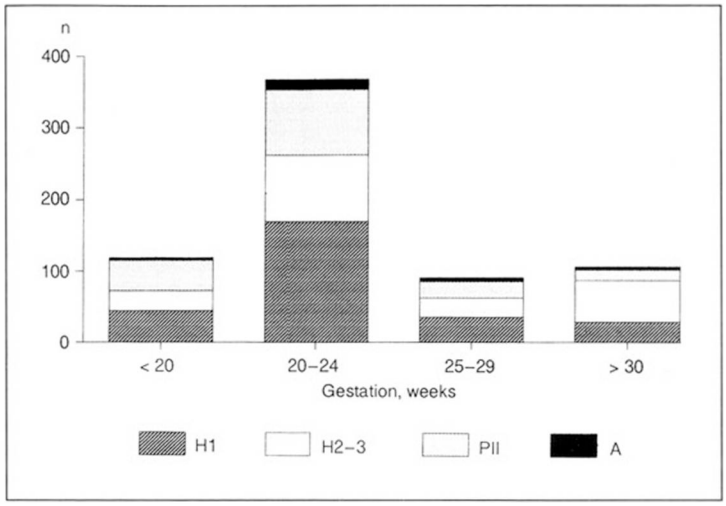

Fig. 1. Gestational age distribution, at the time of referral, of the fetuses with mild hydronephrosis (H1), moderate/severe hydronephrosis (H2–3), multicystic dysplasia (PII), and renal agenesis (A).

The aim of this study was to determine the incidence of chromosomal abnormalities in a large series of antenatally diagnosed renal defects, including mild hydronephrosis, moderate/severe hydronephrosis, multicystic dysplasia and renal agenesis. Detailed ultrasound examination and fetal karyotyping were carried out to investigate whether the risk of chromosomal abnormalities was related to: (i) maternal age; (ii) the unilateral or bilateral nature of renal defects; (iii) the level of the urinary tract obstruction in obstructive uropathy, and (iv) the presence of malformations in other organ systems.

Patients and Methods

During a 6-year period (1985–1990), fetal blood karyotyping was performed in 682 patients with fetal renal defects. All patients were referred from other centres for further assessment of ultrasonographically detectable fetal malformations. The mean gestational age at referral was 24 weeks (fig. 1).

Detailed ultrasound examination was performed for the detection of fetal malformations (Aloka SSD-650 or Hitachi EUB 340, 3.5- or 5-MHz curvilinear transducer). Subsequently, the parents gave informed consent for rapid fetal karyotyping, which was performed by cytogenetic analysis of fetal blood obtained by cordocentesis.

The renal defects, which were either unilateral (n = 172) or bilateral (n = 510), were classified as: (i) mild hydronephrosis (n = 276), when only the renal pelvis was dilated and both the bladder and amniotic fluid volume were normal; (ii) moderate to severe hydronephrosis (n = 206), with varying degrees of pelvic calyceal dilatation; (iii) multicystic dysplasia (n = 173), with multiple non-communicating cysts of variable size and irregular hyperechogenic stroma, and (iv) renal agenesis (n = 27). In the fetuses with bilateral moderate/severe hydronephrosis and multicystic kidneys, the obstruction was considered to be either low (n = 156, dilated bladder) or high (n = 67, bladder normal or empty) and there was either oligohydramnios (n = 120) or the amniotic fluid volume was normal/reduced (n = 103).

The results of the ultrasound examinations and fetal karyotype were given to the referring obstetricians who undertook the further management of the patients. Details on the outcomes of pregnancies were obtained from the referring hospitals.

Results

The fetal karyotype was abnormal in 12% (85 of 682) of the cases. The male to female ratio was 492:190 but the incidence of chromosomal abnormalities was 18% (78 of 190)

Table 2. Abnormal fetal karyotype in 682 fetuses with bilateral or unilateral renal abnormalities, which were either isolated or associated with additional malformations

Renal defect	Cases	Chromosomal abnormalities								
		total	triploidy	autosomal chromosomes					sex chromosomes	
				trisomies				deletions		
				21	18	13	other		45X0	47XYY
Total	682	85 (12%)	5	19	20	18	6	9	6	2
Isolated	476	16 (3%)	2	3	–	1	4	4	–	2
Other	206	69 (34%)	3	16	20	17	2	5	6	–
Bilateral	510	66 (13%)	2	19	15	13	6	6	4	1
Isolated	342	14 (4%)	2	3		1	4	3	–	1
Other	168	52 (31%)	–	16	15	12	2	3	4	–
Mild hydronephrosis	258	35 (14%)	–	15	6	8	3	2	1	–
Isolated	163	5 (3%)	–	1	–	–	3	1	–	–
Other	95	30 (32%)	–	14	6	8	–	1	1	–
Moderate hydronephrosis	119	15 (13%)	1	3	3	2	2	1	3	–
Isolated	81	5 (6%)	1	2	–	–	1	1	–	–
Other	38	10 (26%)	–	1	3	2	1	–	3	–
Multicystic kidneys	109	13 (12%)	1	1	6	2	–	3	–	–
Isolated	79	3 (4%)	1	–	–	1	–	1	–	–
Other	30	10 (33%)	–	1	6	1	–	2	–	–
Renal agenesis	24	3 (13%)	–	–	–	1	1	–	–	1
Isolated	19	1 (5%)	–	–	–	–	–	–	–	1
Other	5	2 (40%)	–	–	–	1	1	–	–	–
Unilateral	172	19 (11%)	3	–	5	5	–	3	2	1
Isolated	134	2 (2%)	–	–	–	–	–	1	–	1
Other	38	17 (45%)	3	–	5	5	–	2	2	–
Mild hydronephrosis	18	2 (11%)	–	–	1	–	–	–	1	–
Isolated	10	0 (0%)	–	–	–	–	–	–	–	–
Other	8	2 (25%)	–	–	1	–	–	–	1	–
Severe hydronephrosis	87	8 (9%)	1	–	1	3	–	3	–	–
Isolated	76	1 (1%)	–	–	–	–	–	1	–	–
Other	11	7 (64%)	1	–	1	3	–	2	–	–
Multicystic kidneys	64	8 (13%)	2	–	2	2	–	–	1	1
Isolated	48	1 (2%)	–	–	–	–	–	–	–	1
Other	16	7 (44%)	2	–	2	2	–	–	1	–
Renal agenesis	3	1 (33%)	–	–	1	–	–	–	–	–
Isolated	0	0 (0%)	–	–	–	–	–	–	–	–
Other	3	1 (33%)	–	–	1	–	–	–	–	–

Table 3. Abnormal karyotype in fetuses with bilateral moderate/severe hydronephrosis or multicystic kidneys in relation to the level of urinary tract obstruction (high or ureteric, and low or urethral), and to the presence or absence of amniotic fluid (AF)

Renal defect H1P+PII+H2–H3	Cases	Chromosomal abnormalities								
		total	triploidy	autosomal chromosomes					sex chromosomes	
				trisomies				deletions		
				21	18	13	other		45X0	other
High obstruction	67	6 (9%)	–	1	–	–	1	1	3	–
Isolated	46	– (0%)	–	–	–	–	–	–	–	–
Other	21	6 (29%)	–	1	–	–	1	1	3	–
Low obstruction	156	22 (14%)	2	3	9	4	1	3	–	–
Isolated	114	8 (7%)	2	2	–	1	1	2	–	–
Other	42	14 (33%)	–	1	9	3	–	1	–	–
AF present	103	14 (14%)	1	2	7	3	–	1	–	–
Isolated	65	3 (5%)	1	1	–	1	–	–	–	–
Other	38	11(29%)	–	1	7	2	–	1	–	–
AF absent	120	14 (12%)	1	2	2	1	2	3	3	–
Isolated	95	5 (5%)	1	1	–	–	1	2	–	–
Other	25	9 (36%)	–	1	2	1	1	1	3	–

in females and 10% (128 of 492) in males. The incidence of chromosomal abnormalities was similar in the four groups of renal defects and in fetuses with bilateral or unilateral renal involvement (table 2). Furthermore, in the fetuses with bilateral moderate/severe hydronephrosis or multicystic kidneys, the incidence of chromosomal abnormalities was similar in the groups with low and high obstruction and in those with oligohydramnios (no vertical pool of amniotic fluid > 1 cm) or normal/reduced amniotic fluid volume (table 3).

The most frequently found chromosomal abnormalities were trisomy 21 (22%), trisomy 18 (24%) and trisomy 13 (21%). Trisomy 21 accounted for 41% of the chromosomal abnormalities found in fetuses with mild hydronephrosis, but for only 8% of the chromosomal abnormalities found in fetuses with moderate/severe hydronephrosis, multicystic dysplasia, or renal agenesis. In the latter three groups, the commonest (48%) chromosomal abnormalities were trisomies 13 and 18.

The patterns of associated malformations are illustrated in table 4. There were: 68 fetuses with brain abnormalities; 38 with facial defects; 57 with nuchal cystic hygromata or nuchal edema; 37 with hydrops; 50 with pulmonary or cardiac defects; 41 with gastrointestinal or abdominal wall defects, and 68 fetuses had skeletal defects including skeletal dysplasia in 7 and abnormalities of the extremities in 63 (talipes n = 26, rocker bottom feet n = 8, sandal gap n = 6, overlapping fingers n = 19, clinodactyly of the fifth finger n = 11, polydactyly n = 2, and syndactyly n = 2).

Abnormal karyotypes were more commonly encountered when there was ultrasonographic evidence of multiple malformations (33%, 69 of 206 cases), than with isolated

Table 4. Chromosomal abnormalities and associated malformations in fetuses with renal defects

	Total	Brain						Face				Neck		
		n	CPC	PFC	Ho	Ve	Enc	n	Cl	Mi	Ma	n	Ne	CyHy
Karyotype														
Normal	597	43	19	2	6	14	2	14	4	10	–	31	29	2
Abnormal	85	25	9	8	11	1	1	24	14	10	3	26	20	12
Trisomies														
22	1	–	–	–	–	–	–	–	–	–	–	–	–	–
21	19	–	–	–	–	–	–	3	–	–	3	11	11	–
18	20	10	8	2	1	–	–	7	3	5	–	1	1	1
13	18	11	–	4	10	1	–	12	10	4	–	5	5	5
12	1	–	–	–	–	–	–	–	–	–	–	–	–	–
9	1	1	–	1	–	–	–	1	–	1	–	–	–	–
8	1	–	–	–	–	–	–	–	–	–	–	–	–	–
Marker	1	–	–	–	–	–	–	–	–	–	–	–	–	–
47XYY	2	–	–	–	–	–	–	–	–	–	–	–	–	–
45X	6	–	–	–	–	–	–	–	–	–	–	6	1	5
Triploidy	5	–	–	–	–	–	–	–	–	–	–	1	–	1
Deletions														
14qT14,21	1	1	1	–	–	–	–	–	–	–	–	1	1	–
14qT13,14	1	1	–	1	–	–	–	1	1	–	–	1	1	–
7q	1	–	–	–	–	–	–	–	–	–	–	–	–	–
2q	2	1	–	–	–	–	1	–	–	–	–	–	–	–
3p	1	–	–	–	–	–	–	–	–	–	–	–	–	–
4p	1	–	–	–	–	–	–	–	–	–	–	–	–	–
5p	1	–	–	–	–	–	–	–	–	–	–	–	–	–
6p	1	–	–	–	–	–	–	–	–	–	–	–	–	–

Associated malformations include: choroid plexus cysts (CPC); posterior fossa cyst (PFC); holoprosencephaly (Ho); ventriculomegaly (Ve); encephalocele (Enc); facial cleft (Cl); micrognathia (Mi); macroglossia (Ma); nuchal oedema (Ne); cystic hygromata (CyHy); hydrops (Hydr); diaphragmatic hernia (DH);

renal defects (3%, 16 of 476 cases). Indeed, in 3 of the latter cases additional malformations were detected at postmortem or postnatal examination; these included imperforate anus in 2, and cardiac defect in 1.

The mean maternal age of the chromosomally abnormal fetuses (31 years, range 19–44) was significantly higher ($t = 4.36$, $p < 0.0001$) than that of the chromosomally normal fetuses (28 years, range 16–45). The maternal age-related risk for fetal chromosomal abnormalities, in our study group, in comparison to that reported in the literature for women undergoing second trimester amniocentesis for advanced maternal age [14], is illustrated in figure 2. The maternal age-related risk in the literature for amniocentesis is 1% at 35–36 years, 1.3% at 37–38 years, 2% at 39–40 years and 3.9% at 41 years or more. In our group, the risk was three times as high when there

Hydr	Chest				Abdomen					Skeletal			
	n	DH	CA	HD	n	DA	EA	Ex	Ac	n	Dys	Extr	
													Karyotype
27	18	3	2	15	21	–	3	9	9	37	7	32	Normal
10	32	4	–	30	20	2	7	13	–	31	–	31	Abnormal
													Trisomies
–	–	–	–	–	–	–	–	–	–	–	–	–	22
1	3	–	–	3	3	2	1	–	–	6	–	6	21
1	12	3	–	11	11	–	5	9	–	13	–	13	18
1	8	1	–	7	3	–	1	2	–	9	–	9	13
–	–	–	–	–	–	–	–	–	–	–	–	–	12
–	1	–	–	1	–	–	–	–	–	–	–	–	9
–	–	–	–	–	–	–	–	–	–	–	–	–	8
–	–	–	–	–	1	–	–	1	–	–	–	–	Marker
–	–	–	–	–	–	–	–	–	–	–	–	–	47XYY
5	5	–	–	5	–	–	–	–	–	–	–	–	45X
1	1	–	–	1	–	–		–	–	1	–	1	Triploidy
													Deletions
1	1	–	–	1	–	–	–	–	–	–	–	–	14qT14,21
–	1	–	–	1	1	–	–	1	–	1	–	1	14qT13,14
–	–	–	–	–	–	–	–	–	–	–	–	–	7q
–	–	–	–	–	–	–	–	–	–	–	–	–	2q
–	–	–	–	–	–	–	–	–	–	–	–	–	3p
–	–	–	–	–	–	–	–	–	–	–	–	–	4p
–	–	–	–	–	1	–	–	1	–	–	–	–	5p
–	–	–	–	–	–	–	–	–	–	1	–	1	6p

cystic adenomatoid malformation (CA); heart defect (HD); duodenal atresia (DA); esophageal atresia (EA); exomphalos (Ex); abdominal cysts (Ac); skeletal dysplasias (Dys), and abnormalities of the extremities (Extr).

was an isolated renal defect and thirty times as high when there were additional malformations.

In the 276 fetuses with mild hydronephrosis, the biparietal diameter to femur length ratio (BPD/FL) was compared to the normal mean for gestation, established from the cross-sectional study of 1,050 normal fetuses from singleton pregnancies (fig. 3). The mean BPD/FL in the 15 fetuses with trisomy 21 and in the 22 with chromosomal abnormalities other than trisomy 21 was significantly higher than the normal mean for gestation (mean difference = 0.699, SEM = 0.267, $t = 2.62$, $p < 0.05$, and mean difference = 1.088, SEM = 0.386, $t = 2.82$, $p < 0.05$, respectively). The BPD/FL was above the 95th percentile in 7% (16 of 239) of the chromosomally normal fetuses, 7% (1) of fetuses with trisomy 21, and in 32% (7) of those with chromosomal abnor-

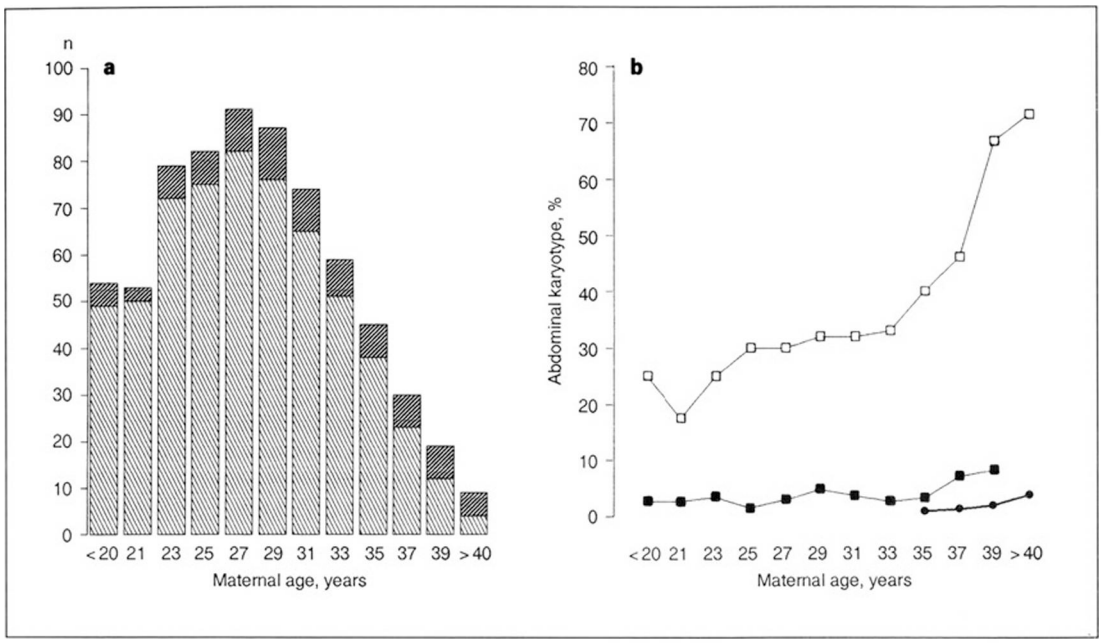

Fig. 2. **a** Maternal age distribution of chromosomally normal (▨) and abnormal (▨) fetuses. **b** Maternal age-related risk for chromosomal abnormalities in the presence of fetal renal defects only (■) and in the presence of multiple defects (□) compared to the overall maternal age-related risk (●) derived from data of women undergoing amniocentesis [14].

malities other than trisomy 21. All 8 chromosomally abnormal fetuses with BPD/FL above the 95th percentile (trisomy 21 n = 1, trisomy 18 n = 2, trisomy 13 n = 1, partial trisomy 12 n = 1, deletion 14q n = 1, Turner's syndrome n = 2) had multiple defects. The BPD/FL was not examined in fetuses with other renal defects because in the presence of the commonly associated oligohydramnios and consequent dolichocephaly (decreased BPD), no valid conclusions can be drawn.

Discussion

This study has established that, when fetal renal defects are detected by ultrasonographic examination, the risk for fetal chromosomal abnormalities is dramatically increased over the maternal age-related risk; threefold when the renal defect is isolated and thirtyfold when there are multiple defects. The risk of chromosomal abnormalities is similar for fetuses with: (i) unilateral or bilateral involvement; (ii) mild hydronephrosis, moderate/severe hydronephrosis, multicystic kidneys, or renal agenesis; (iii) urethral or ureteric obstruction, and (iv) oligohydramnios or normal/reduced amniotic fluid volume. Furthermore, the majority (71%) of the fetuses with renal defects we have examined were male but, in females, the risk of chromosomal abnormality was almost twice as high as in males.

The patterns of chromosomal abnormalities were related to the different types of renal defects. In mild hydronephrosis, the commonest chromosomal abnormality was tri-

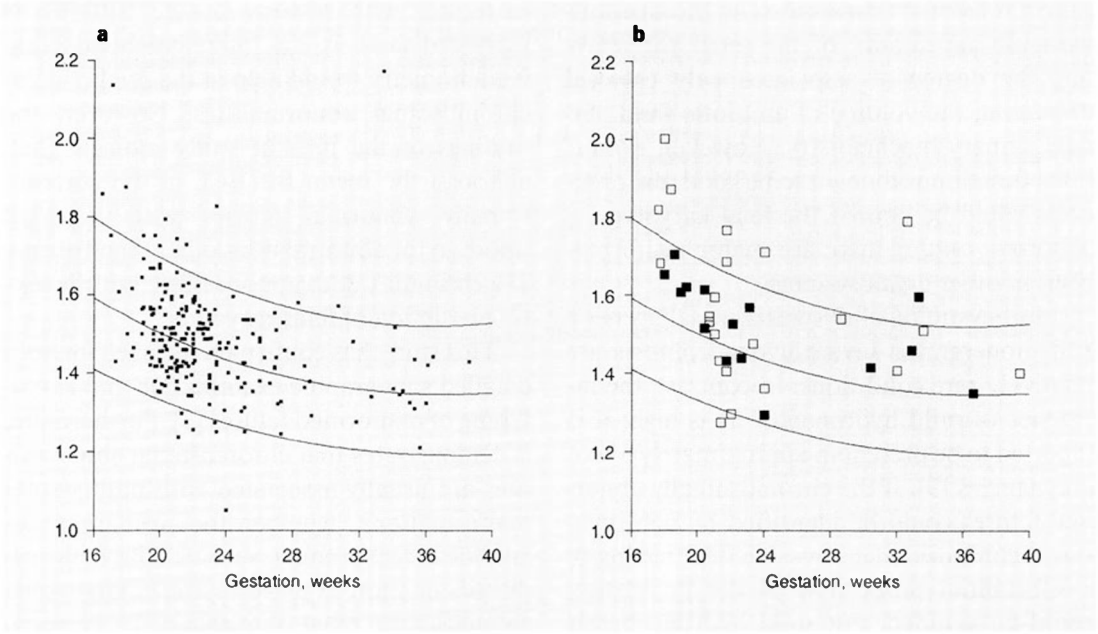

Fig. 3. Biparietal diameter to femur length ratio in fetuses with mild hydronephrosis that were chromosomally normal (**a**) or abnormal (**b**). ■ = Trisomy 21; □ = other chromosomal abnormalities.

somy 21, whereas in moderate/severe hydronephrosis, multicystic kidneys or renal agenesis the commonest abnormalities were trisomies 18 and 13, each with their own syndromal defects. Consequently, the patterns of associated malformations were different [1]. For example, in trisomy 13 the most commonly encountered defects were holoprosencephaly, facial cleft, cardiac defects and abnormalities of the hands and feet. In trisomy 18, associated malformations included choroid plexus cysts, facial cleft or micrognathia, heart defects, exomphalos, overlapping fingers and talipes. In contrast, in trisomy 21 the associated defects were more subtle and included nuchal edema, macroglossia, sandal gap and clinodactyly.

Bilateral renal agenesis and multicystic renal dysplasia are lethal abnormalities. Fetal karyotyping in these conditions is essential for accurate counselling of parents about the etiology of the condition and the risk of recurrence. When chromosomal abnormalities such as primary trisomies are present, the risk of recurrence is approximately 1%. For chromosomal rearrangements or deletions it is important to check that they are not secondary to parental chromosomal rearrangements. In the group without chromosomal abnormalities but with multiple malformations, the risk of recurrence may be much higher because the condition may be due to a genetic syndrome with an autosomal recessive mode of inheritance.

In fetuses with moderate or severe hydronephrosis, antenatal investigations are aimed at both defining prognosis for the present pregnancy and the risk of recurrence. Predic-

tion of renal function is based on the ultrasonographic appearance of the renal parenchyma, the degree of associated pelvi-calyceal dilatation, the volume of amniotic fluid and fetal urinary biochemistry. However, even if renal function is thought to be good, the prognosis could be poor if the fetal karyotype is abnormal and/or there are major malformations in other organ systems.

Multicystic renal dysplasia, renal agenesis and moderate or severe hydronephrosis are relatively rare conditions. In contrast, the incidence of mild hydronephrosis is high; it is reported to be present in approximately 3% of pregnancies [9]. If the chromosomally abnormal fetuses could be identified by non-invasive techniques, then invasive fetal testing in a substantial proportion of the population could be avoided. For mild hydronephrosis the most frequently encountered chromosomal abnormality is trisomy 21 in which the associated fetal malformations are subtle and their detection is difficult even in specialist centres. Previous studies have reported that in fetuses with trisomy 21 the BPD/FL is increased [15]. It was therefore hoped that fetal biometry would help in the prediction of chromosomal abnormalities. However, the findings of the present study indicate that, although the mean BPD/FL of the chromosomally abnormal fetuses was increased (more so for abnormalities other than trisomy 21), this index does not provide clinically useful prediction of fetal karyotype.

This study has confirmed the need for both detailed sonographic examination and karyotyping of malformed fetuses [3]. Furthermore, it demonstrates that chromosomal abnormalities are usually associated with multisystem malformations, whether the primary sonographic defect is small, such as mild hydronephrosis or choroid plexus cysts, or large, such as multicystic renal dysplasia or holoprosencephaly [16, 17]. Nevertheless, even with small isolated defects, such as mild hydronephrosis, the parents should be counselled that their age-related risk for chromosomal abnormalities is increased.

References

1 Smith DW: Recognizable Patterns of Human Malformation. Philadelphia, Saunders, 1982.

2 Curry CJR, Jensen K, Holland J, Miller L, Hall BD: The Potter sequence: A clinical analysis of 80 cases. Am J Med Genet 1984;19: 679–702.

3 Nicolaides KH, Rodeck CH, Gosden CM: Rapid karyotyping in non-lethal fetal malformations. Lancet 1986;i:283–286.

4 Rizzo N, Gabrielli S, Pilu G, Perolo A, Cacciari A, Domini R, Bovicelli L: Prenatal diagnosis and obstetrical management of multicystic dysplastic kidney disease. Prenat Diagn 1987;7:109–118.

5 Boue A, Muller F, Briard ML, Boue L: Interest of biology in the management of pregnancies where a fetal malformation has been detected by ultrasonography. Fetal Ther 1988;3: 14–23.

6 Hegge FN, Prescott GH, Watson PT: Sonography at the time of genetic amniocentesis to screen for fetal malformations. Obstet Gynecol 1988;71:522–525.

7 Reuss A, Wladimiroff JW, Stewart PA, Scholtmeijer RJ: Non-invasive management of fetal obstructive uropathy. Lancet 1988;ii:949–951.

8 Eydoux P, Choiset A, Le Porrier N, Thepot F, Szpiro-Tapia S, Allict J, Ramond S, Viel JF, Gautier E, Morichon N, Girard-Orgeolet S: Chromosomal prenatal diagnosis: Study of 936 cases of intrauterine abnormalities after ultrasound assessment. Prenat Diagn 1989;9:255–269.

9 Benacerraf BR, Mandell J, Estroff JA, Harlow BL, Frigoletto FD: Fetal pyelectasis: A possible association with Down syndrome. Obstet Gynecol 1990;76:59–60.

10 Holzgreve W, Miny P, Gerlach B, Westendorp A, Ahlert D, Horst J: Benefits of placental biopsies for rapid karyotyping in the second and third trimesters (late chorionic villus sampling) in high risk pregnancies. Am J Obstet Gynecol 1990; 162:1188–1192.
11 Rizzo N, Pittalis MC, Pilu G, Orsini LF, Perolo A, Bovicelli L: Prenatal karyotyping in malformed fetuses. Prenat Diagn 1990;10:17–23.
12 Shah DM, Roussis P, Ulm J, Jeanty P, Boehm FH: Cordocentesis for rapid karyotyping. Am J Obstet Gynecol 1990;162:1548–1550.
13 Stoll C, Alembik Y, Roth MP, Dott B, Sauvage P: Risk factors in internal urinary system malformations. Pediatr Nephrol 1990;4:319–323.
14 Ferguson-Smith MA, Yates JRW: Maternal age specific rates for chromosome aberrations and factors influencing them: Report of a collaborative European study on 52,965 amniocentesis. Prenat Diagn 1984; 4:5.
15 Lockwood C, Benacerraf B, Krinsky A, Blakemore K, Belanger K, Mahoney M, Hobbins J: A sonographic screening method for Down syndrome. Am J Obstet Gynecol 1987; 157:803–808.
16 Thorpe-Beeston JG, Gosden CM, Nicolaides KH: Choroid plexus cysts and chromosomal defects. Br J Radiol 1990;63:783–786.
17 Berry SM, Gosden C, Snijders RJM, Nicolaides KH: Fetal holoprosencephaly: Associated malformations and chromosomal defects. Fetal Diagn Ther 1990;5:92–99.