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The association of aneuploidy and mild fetal pyelectasis in an unselected population: the results of a multicenter study

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ABSTRACT

Introduction *Mild pyelectasis is a common finding and there is some debate as to its association with aneuploidy. The results of a large, prospective, multicenter study of mild pyelectasis designed to determine the incidence and association with aneuploidy in an unselected population are reported.*

Methods *A large multicenter, prospective observational study of unselected fetuses with mild pyelectasis identified between 16 and 26 weeks' gestation in routine ultrasound departments.*

Results *There were 737 fetuses with mild pyelectasis of which 12 had an abnormal karyotype. Pyelectasis was isolated in three fetuses with Down syndrome, but in one the mother was older (36 years).*

Conclusion *These data confirm the fact that the presence of mild fetal pyelectasis increases the risk for aneuploidy, in particular trisomy 21. However, other risk factors should be considered before embarking on fetal karyotyping, as for most pregnancies complicated by isolated mild pyelectasis, risks of aneuploidy will remain small.*

INTRODUCTION

The association of aneuploidy with mild dilatation of the fetal renal pelvis was first reported in 1990 by Benacerraf *et al.*, who noted that, of 210 fetuses with pyelectasis, seven had Down's syndrome[1]. Others have subsequently confirmed this association[2–5] with occasional studies reporting no association[6]. However, many studies are small[4–6], report data from selected populations[1,2,6] and make no allowance for other risk factors such as maternal age (Table 1). We report the results of a large, prospective, multicenter study designed to determine the incidence and association with aneuploidy of mild pyelectasis in an unselected population.

METHODS

Cases were recruited from 13 obstetric units (Table 2). Only women attending for routine antenatal care were included. One of the authors (P.C.) visited all units on a regular basis to ensure conformity of recruitment and to assist with data collection. Several of the hospitals involved in the study also acted as fetal ultrasound referral units. Patients referred from other hospitals to these centers were excluded. Down syndrome screening was not consistent across these units, with some offering second-trimester serum screening, but none offering first-trimester screening.

For the purposes of this study mild pyelectasis was defined as an antero-posterior diameter of the renal pelvis of 5 mm up to and including 10 mm. All fetuses of between 16 and 26 weeks' gestation with either unilateral or bilateral pyelectasis were recruited. Gestational age was confirmed or assigned by crown–rump length measurement in the first trimester or by measurement of the biparietal diameter, head circumference and femur length in the second trimester. Following the discovery of mild pyelectasis a detailed fetal anatomical examination was performed to detect any other abnormalities or markers of aneuploidy, including increased nuchal fold, ventriculomegaly, choroid plexus cysts, echogenic bowel or cardiac focus, short femora, clinodactyly and sandal gap. Maternal age was recorded in all cases. Raised maternal age was defined as ≥ 36 years at the estimated date of delivery. Fetuses with coexistent renal anomalies at the time of recruitment were excluded. Fetal and maternal details were recorded on a specifically designed data sheet, independently from the hospital notes, and subsequently entered onto a computerized database. In centers where hard copy recording facilities were available images of all kidneys with a dilated pelvis were recorded and stored with the data sheet for review at a later stage.

The section selected for measurement of the right pelvis was obtained separately from that selected for measurement of the left pelvis in all cases. Measurements were taken as follows: a transverse section of the fetal abdomen was obtained and one kidney identified in cross section. The transverse section of the kidney demonstrating the largest renal pelvis was assessed visually. The antero-posterior diameter of the pelvis was obtained by placing the calipers on the inner borders of the renal pelvis. The process was then repeated for the contralateral kidney and pelvis.

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Table 1 Summary of literature on the association between mild pyelectasis and aneuploidy

Author	*Year*	*Population*	*Gestational age (weeks)*	*Total population*	*No. with MP*	*Incidence (%)*	*Size*	*Karyotype for isolated MP*		*Karyotype for MP and other abnormalities*	
								Normal	*Abnormal*	*Normal*	*Abnormal*
Benacerraf *et al.*[1]	1990	N/K	16–40	7 400	210	2.8	AP ≥ 4 mm 15–20 weeks AP ≥ 5 mm 20–30 weeks AP ≥ 7 mm 30–40 weeks	203	7 Trisomy 21		
[a]Corteville *et al.*[3]	1992	Mixed	14–40	5 944	127	2.1	AP ≥ 4 mm ≤ 33 weeks AP ≥ 7 mm ≥ 33 weeks	N/S	1 Trisomy 21	N/S	3 Trisomy 21 3 other
Nicolaides *et al.*[2]	1992	Selected	15–38	N/K	258		≥ 5 mm	158	5 (1 Trisomy 21 4 other)	65	30 Trisomies 21, 13, 18, other
Wickstrom[9]	1996	N/K	17–39	11 340	82	0.72	AP ≥ 4–10 mm	79	3 Trisomy 21		
Wickstrom[5]	1996	Selected	≥ 15	7 481	121	1.6	AP ≥ 4 mm < 33 weeks AP ≥ 7 mm > 33 weeks	121	2 Trisomy 21 1 mosaic 46,XY/47,XYY		
[b]Ouzounian *et al.*[4]	1996	N/K			84		AP ≥ 4 mm	N/S	0	N/S	1 Trisomy 21
[c]This study		Unselected	16–26	101 600	737	0.73	AP ≥ 5–10 mm	648	3 Trisomy 21	89	3 Trisomy 21 1 Trisomy 13 1 Trisomy 8 2 45,XO 2 other
Total								1209	22 (1.8%)		

[a] States that from her data predictive value is 1 : 340 for isolated MP; [b] retrospective review of all cases with MP; [c] based on phenotype as not all were formally karyotyped; AP, antero-posterior; MP, mild pyelectasis; N/K, not known; N/S, not stated.

Table 2 Hospitals participating in the study showing number of deliveries and cases with pyelectasis recruited

Hospital	*Number of deliveries*	*Number recruited*	*Incidence (%)*
Guy's	6 715	76	1.13
King's College	9 545	91	0.95
Luton & Dunstable	11 402	43	0.38
Northwick Park	8 210	34	0.41
Plymouth General	15 358	56	0.36
Watford General	7 500	43	0.57
Southmead	9 374	12	0.13
Bristol Maternity	8 191	52	0.63
Hillingdon	8 550	182	2.13
Colchester	3 851	31	0.80
West London	1 668	15	0.90
Derby City	7 600	84	1.11
University College	3 636	18	0.50
Total	101 600	737	0.73

Fetuses were re-scanned every 4–6 weeks. Karyotyping was performed according to local practice and not routinely as it was accepted that the majority of clinically significant chromosomal abnormalities are manifest shortly after birth. Details of the pregnancy outcomes were sought from the maternity units in the first instance. Where follow-up was unsuccessful the general practitioners and women themselves were approached by letter. The majority of neonates were followed up for 1 year as part of a study to determine the clinical significance of prenatally detected mild pyelectasis (details to be published elsewhere).

It was not possible to ascertain the exact number of fetuses scanned in the period of the study. As more than 95% of women in the participating centers underwent a second-trimester anomaly ultrasound examination the total population scanned was estimated from the number of births in each center.

RESULTS

There were 737 fetuses with mild pyelectasis amongst a total of 101 600 births, giving an incidence of 0.73% (95% confidence intervals (CI) 0.13, 1.33). The incidence in individual centers varied from 0.13 to 2.13% (Table 2). The dilatation was bilateral in 506 and unilateral in 231 fetuses. In 637 fetuses the pyelectasis was an isolated finding and in 100 cases other risk factors (sonographic abnormalities or maternal age ≥ 36 years at delivery) were present (Table 3). Outcome data were available in 704 of the 737 cases; 31 of the cases with isolated pyelectasis and two with other risk factors (one raised maternal age and one with an increased nuchal fold) were lost to follow-up. In cases where outcome was determined, there was a total of 23 (3.27%) deaths (including six terminations of pregnancy) and one spontaneous abortion at 22 weeks' gestation (Table 4).

The distribution of gestational ages at recruitment is shown in Table 5, with 76.9% of cases presenting between 17 and 22 weeks.

There were 12 abnormal karyotypes (Tables 3 and 4), six cases of trisomy 21, one case of trisomy 13, one trisomy 8, two

Table 3 Karyotype of fetuses with mild pyelectasis and additional risk factors or other sonographic findings

	Karyotype	
Additional risk factors	*Normal*	*Abnormal*
RMA*	44	1 Trisomy 21
RMA and CPCs		1 47,XXX
RMA and sandal gap		1 Trisomy 21
CPCs	25	
CPCs and sandal gap	1	
CPCs and bright kidneys	1	
Increased nuchal fold*	11	1 Trisomy 21
Increased nuchal fold and short limbs	1	
Sandal gap	4	
Bright kidneys		1 45,XO
Unilateral multicystic kidney	1	
Cystic hygroma		1 Trisomy 21 1 45,XO
Mild cerebral ventriculomegaly	1	1 Trisomy 8
Cerebral ventriculomegaly and cleft lip		1 Trisomy 13
Ventriculoseptal defect		1 46,XX1q +
Right-sided stomach	1	
Total	90	10

RMA, maternal age ≥ 36 years; CPCs, choroid plexus cysts; *1 case lost to follow up.

Turner's syndrome, one unbalanced translocation and one triple X (47,XXX). Nine of these had associated sonographic abnormalities detected in the second trimester (Tables 3 and 4), one occurred in a case with isolated pyelectasis where the maternal age was increased (36 years) and the remaining two were associated with isolated pyelectasis in pregnancies of younger women (23 and 33 years). The distribution of maternal ages in pregnancies complicated by mild pyelectasis is shown in Table 6. Abnormal karyotypes were found in fetuses with unilateral (n = 3) and bilateral (n = 9) pyelectasis.

The overall incidence of aneuploidy in fetuses with pyelectasis was 1.70% (95% CI 0.88, 2.98) (Table 7). In fetuses where pyelectasis was the only sonographic abnormality seen the incidence of proven aneuploidy was 0.46% (95% CI 0.09, 1.35). Where other sonographic abnormalities were found the incidence was 9.18% (95% CI 4.29, 16.72). In the series reported here, we consider that the numbers are insufficient to stratify risk by taking account of maternal age as a continuous variable. Thus we have also analysed the data taking a maternal age ≥ 36 years at delivery to be an additional risk factor. When taking this into consideration, the risk of aneuploidy in the presence of isolated pyelectasis in women ≤ 35 years at delivery is 1 in 303 or 0.33% (95% CI 0.039, 1.19). In women ≥ 36 years the risk of aneuploidy in the presence of isolated pyelectasis increases to 1 in 45 or 2.22% (95% CI 0.06, 11.77).

In this series there was one termination of pregnancy for a fetus with hydrocephalus, where karyotyping was not performed (case 15, Table 4). In view of the possibility of aneuploidy in this case, the incidence of aneuploidy has also been calculated making the assumption that this fetus had an abnormal karyotype. Thus basing the calculation on 13 aneuploid fetuses rather than 12 the incidence of aneuploidy

Table 4 Summary of abnormal pregnancy outcomes

Case No.	Maternal age (years)	Renal pelvis dilation		Gestational age (weeks)	Other sonographic findings	Outcome	Postmortem	Postnatal findings	Karyotype
		Max. diam (mm)	Type						
1	36	7, 7	Bi	19+	—	A/W	—	—	47,XX + 21
2	26	7.5, 8	Bi	20	NF	TOP	—		47,XY + 21
3	38	5	Uni	25+	Sandal gap	IUD	—	Hydropic	47,XY + 21
4	23	5, 7.5	Bi	19+	—	A/W	—		47,XY + 21
5	33	8.5, 6	Bi	20	Cystic hygroma	TOP	—		47,XY + 21
6	33	7, 6	Bi	23+	—	A/W	—		47,XX + 21
7	27	5	Uni	19+	Hydrocephalus CL & P	NND	—		47,XX + 13
8	23	10, 9.5	Bi	25+	Hydrocephalus	TOP	✔	Confirmed	47,XY + 8
9	35	8.5	Uni	22+	Bright kidneys, decreased AF	SB 35 weeks	—		45,X0
10	25	9, 8	Bi	17+	Cystic hygroma, pleural effusions	TOP	✔	Confirmed	45,X0
11	37	6.5, 5.5	Bi	18+	CPCs	LB	—		47,XXX
12	29	7, 5.5	Bi	23+	Hypoplastic left heart	TOP	✔	Confirmed	46,XX1q +
13	35	5.5, 5.5	Bi	—	—	SA 22 weeks	—	—	—
14	29	6, 5	Bi	—	20-week size	IUD 27 weeks	✔	Normal	46,XX
15	34	?	Bi	—	Hydrocephalus	TOP	✔	Confirmed	
16	27	5	Uni	—	CPCs	APH 29 weeks	✔	Normal (maternal rheumatoid)	—
17	35	6	Uni	—	—	IUD 27 weeks	✔	Asymmetrical IUGR	—
18	22	5, 5.5	Bi	—	—	SB 32 weeks	—	No abnormalities detected	46,XY
19	28	6.5, 7	Bi	—	—	APH 32 weeks	—	CMV	—
20	27	7, 5.5	Bi	—	—	SB 36 weeks	—	Extra finger, otherwise NAD	—
21	22	5	Uni	—	Severe oligo	SB 24 weeks	✔	NAD	—
22	41	6	Uni	—	—	Intrapartum SB	✔	NAD	46,XX
23	34	8, 8	Bi	—	—	NND 25 weeks	✔	NAD	—
24	33	5, 5.5	Bi	—	—	NND	—	Septicemia	—
25	27	5	Uni	—	—	NND 37 weeks	—	Metabolic disease	—
26	21	6.5	Uni	—	—	NND	Lost to FU		
27	26	5	Uni	—	Short limbs, NF	NND	—	Porencephalic cyst	46,XY

Uni, unilateral; Bi, bilateral; A/W, alive and well; CPCs, choroid plexus cysts; NF, increased nuchal fold; CL & P, cleft lip and palate; IUD, intrauterine death; LB, live birth; SB, still birth; NND, neonatal death; TOP, termination of pregnancy; FU, follow up; SA, spontaneous abortion; IUGR, intrauterine growth restriction; NAD, nothing abnormal detected; CMV, cytomegalovirus; oligo, oligohydramnios; APH, antepartum hemorrhage; AF, amniotic fluid.

Table 5 Gestational age at recruitment

Gestational age at recruitment (weeks)	*Number*	*Frequency (%)*
16^0–16^6	16	2.2
17^0–17^6	48	6.5
18^0–18^6	116	15.7
19^0–19^6	173	23.5
20^0–20^6	159	21.6
21^0–21^6	71	9.6
22^0–22^6	48	6.5
23^0–23^6	45	6.1
24^0–24^6	34	4.6
25^0–25^6	24	3.3
26^0	3	0.4
Total	737	

Table 6 Distribution of maternal age in pregnancies complicated by mild fetal pyelectasis

Maternal age (years)	*Study group (%)*	*England and Wales (%)*
< 20	5.1	6.9
20–24	21.8	22.8
25–29	36.7	33.0
30–34	27	28.9
35–39	7.5	7.1
40–44	1.8	1.2
≥ 45	0.1	0.1
≥ 35	9.4	8.4

Based on 737 women recruited to the study and 2 565 778 women delivered of live births in England and Wales (HMSO 1996).

Table 7 Incidence of aneuploidy in our study for various classifications of 704 of 737 fetuses with follow-up

Sonographic finding	*Maternal age (years)*	*Number*	*Risk (%)*	*95% CI*
Pyelectasis	All	12/704	1.70 (1.84)	0.88, 2.98
Isolated pyelectasis	All	3/651	0.46	0.095, 1.35
Isolated pyelectasis	< 36	2/606	0.33	0.039, 1.19
Isolated pyelectasis	≥ 36	1/45	2.22	0.06, 11.77
Pyelectasis & other abnormality	All	9/98	9.18 (10.2)	4.29, 16.72
Pyelectasis & other abnormality	< 36	7/46	15.22 (17.4)	6.34, 28.87
Pyelectasis & other abnormality	≥ 36	2/2	100	15.81, 100

The numbers in parentheses represent the risk if the case (15) with abnormal findings at birth but no karyotype recorded is assumed to have an abnormal karyotype.

in fetuses with pyelectasis increases from 1.70 to 1.84% overall (Table 7).

The gender was known in 694 of the 737 cases with mild pyelectasis, with 474 males and 220 females. An abnormal karyotype was found in five of the 474 males (1.05%) and seven of the 220 females (3.18%). This difference was not significant ($P = 0.06$). When sex chromosome anomalies are excluded the incidence of aneuploidy in female fetuses is 1.84%.

DISCUSSION

The mean incidence of pyelectasis in our population is 0.73% (95% CI 0.13, 1.33) which is similar to that reported in the literature (0.72–2.8%) (Table 1). The variation in incidence between study centers is difficult to explain as all centers in the study were using the same diagnostic criteria, but could perhaps reflect differences in ultrasound equipment. The overall incidence of aneuploidy in fetuses with isolated pyelectasis in our series (1 in 217) is considerably less than that reported in most studies in the literature where the incidence varies from 1 in 29[1] to 1 in 60[5]. However, the study of Corteville *et al.*[3] suggests an incidence of 1 in 303 in low risk fetuses with isolated pyelectasis. This compares favorably with the figure of 1 in 324 in our series of fetuses with isolated pyelectasis in mothers under the age of 36 years.

The data in Table 6 shows the distribution of maternal ages in our population. The proportion of older women (9.4% ≥ 35 years) was not significantly greater than the 8.4% reported for pregnancies in general in England and Wales[7]. One criticism of our data is that we do not have details regarding results of other screening tests for Down syndrome. However, the study was carried out before widespread implementation of first-trimester screening, and in many centers, second-trimester serum screening was not routinely performed.

In our study there was a trend towards a higher incidence of aneuploidy in female fetuses with mild pyelectasis, an observation also made by Nicolaides *et al.*[2]. They found abnormal karyotypes in 18% of female compared with 10% of male fetuses. Whilst the difference is not statistically significant, there does appear to be a trend towards an increased risk in female fetuses. Much of the difference in both studies can be attributed to sex chromosome anomalies in female fetuses. If these are excluded then the incidence in the study by Nicolaides falls from 18% to 14%, and in our study from 3.2% to 1.8%.

In the study reported here aneuploidy was found in fetuses with bilateral and unilateral pyelectasis. In the three fetuses that had Down syndrome, and where the pregnancy continued, the degree of renal pelvic dilatation did not change significantly during the pregnancy. In these cases a postnatal renal scan failed to confirm the pyelectasis/demonstrated mild upper tract dilatation, which had resolved spontaneously. One of these babies had an atrial ventricular septal defect diagnosed postnatally. The other two had phenotypic features of Down syndrome, but no other major abnormality.

Down syndrome is the chromosomal abnormality most commonly associated with pyelectasis reported in the literature, although in this study it was associated with six different karyotypes. Six of the 12 aneuploid fetuses (50%) in this study demonstrated a trisomy 21 karyotype. The two cases with isolated mild pyelectasis and the third case of 'isolated' pyelectasis in a mother with raised maternal age (36 years) all demonstrated trisomy 21. Pooling the data from the studies listed in Table 1 and our series provides a total of 17 fetuses with trisomy 21 in 1231 fetuses with isolated mild pyelectasis. This gives an incidence of trisomy 21 in fetuses with pyelectasis of 1 in 72 (1.4%). This figure is greater than would be expected, but includes selected and undefined populations, where the incidence of Down syndrome would be expected to be

increased. Corteville *et al.* reported an incidence of 1 in 340 in unselected pregnancies[3], which is in keeping with our figure of 1 in 303 in low-risk women.

In one case (number 15; Table 4), the pregnancy was terminated because of hydrocephalus and bilateral mild pyelectasis. This fetus was not karyotyped, but aneuploidy should be considered. Taking this into consideration when calculating the incidence of aneuploidy, the overall risk of aneuploidy increases from 1.70% to 1.84% (Table 7), and from 9.18% to 10.2% in fetuses with pyelectasis and other risk factors. There was also one unexplained death (case 20; Table 4) where additional features were found on clinical examination after death. This fetus had an extra digit, but was normally grown and no other anomalies were noted on external examination. Postmortem was declined and karyotyping not done. Aneuploidy is unlikely in this case as polydactyly is a feature of trisomy 13 which is usually associated with poor fetal growth and other anomalies, many of which would be visible on external examination. There were no other cases where the pregnancy ended in a perinatal death with features suggestive of aneuploidy and so the incidence of aneuploidy quoted for our population of fetuses with isolated pyelectasis has not been adjusted for these deaths.

In conclusion, we consider that the evidence presented here in conjunction with that in the literature, shows that the presence of mild pyelectasis increases the risk of aneuploidy, predominantly trisomy 21. Aneuploidy can occur in association with the presence of unilateral or bilateral pyelectasis. Any fetus with pyelectasis should have a detailed ultrasound scan to search for other markers of aneuploidy. We agree with the approach of Snijders and Nicolaides[8] and consider that where the fetus has isolated pyelectasis the woman should be advised that this finding increases her prior risk of aneuploidy. The risk may be slightly greater if the fetus is female, but further data are required to confirm this observation. In the majority of cases the risk will remain very small, being only marginally greater than the mother's age-related risk, and counseling should thus be cautiously optimistic. However, as maternal age increases it seems clear that there is cause for concern. Parents should be advised of the association between mild pyelectasis and aneuploidy and of the difficulties in defining risk and be allowed to decide for themselves whether they wish to proceed to karyotyping. It may well be that with improvements in technology and sonographer awareness, other minor features of aneuploidy will be detected more frequently, thus making our conclusion redundant. It must also be remembered that the widespread implementation of other screening tests for aneuploidy will alter the prevalence of aneuploidy at 18–20 weeks, which will further alter any currently published risk figures for fetuses with mild pyelectasis. Thus there remains a need for further study taking all risk factors, including maternal age, serum biochemistry and first-trimester nuchal translucency measurement, into consideration.

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