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Isolated fetal pyelectasis and chromosomal abnormalities

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KEY WORDS
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Prenatal diagnosis
Fetal ultrasound

Objective: The primary objective of this study was to determine if isolated pyelectasis is a risk factor for trisomy 21.

Study design: Twelve thousand, six hundred and seventy-two unselected singleton fetuses were examined by prenatal ultrasound during the second trimester at a single institution. The sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio of pyelectasis (either isolated or in association with other soft markers/structural anomalies) to detect trisomy 21 were calculated.

Results: Pyelectasis (anteroposterior pelvic diameter $\geq$4 mm) was detected in 2.9% (366/12,672) of the fetuses. Among these, 83.3% (305/366) were isolated, and 16.7% (61/366) were associated with other markers/structural anomalies. The prevalence of trisomy 21 was 0.087% (11/12,672) and, among these fetuses, 2 (18.1%) had pyelectasis, 1 isolated, and 1 associated with other markers/structural anomalies. The presence of isolated pyelectasis had 9.09% sensitivity, 97.6% specificity, 0.33% positive predictive value, and 99.9% negative predictive value to detect fetuses with trisomy 21. The likelihood ratio of trisomy 21 in this group of fetuses was 3.79 (95% CI 0.582–24.616). Among fetuses with pyelectasis and other associated markers/structural anomalies, the sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio for trisomy 21 were 9.09%, 99.5%, 1.64%, 99.9%, and 19.2 (95% CI 2.91–126.44).

Conclusion: In the absence of other findings, isolated pyelectasis is not a justification for the performance of an amniocentesis.

Pyelectasis, which is a dilatation of the renal pelvis visible with ultrasound, is an anatomic variant that rarely has pathologic significance for fetal and postnatal renal function. Generally, the renal pelvis is collapsed and, thus, undetectable with ultrasound.

The renal pelvis diameter may be affected by maternal hydration,[1-3] although this view is not shared by all investigators.[4,5] Persutte et al[6] reported that repeated measurements of the renal pelvis performed within a period of 2 hours present high variability, and that this observation was independent from the maternal hydration status. A possible genetic predisposition to pyelectasis in consecutive pregnancies has been proposed by Degani et al.[7]

In 1990, Benacerraf et al[8] were first to suggest an association between pyelectasis and aneuploidy. They estimated a 3.3% risk for Down syndrome when pyelectasis was present. In this study, we investigated the prevalence and possible association of pyelectasis with

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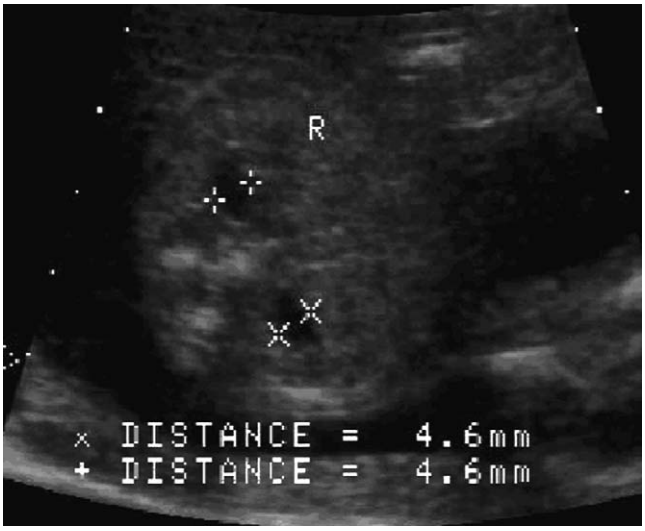

Figure 1 Measurement of the renal pelvis in the anteroposterior dimension in a fetus with bilateral pyelectasis of 4.6 mm.

aneuploidy in an unselected population of patients. We determined whether the finding of fetal pyelectasis in the second trimester justified alteration in patient management, in particular, whether or not patients should be subjected to a karyotype.

Various criteria have been used to define fetal renal pyelectasis. For example, Benacerraf et al defined pyelectasis as a renal pelvis anteroposterior diameter greater or equal to 4 mm in fetuses between 15 and 20 weeks; an anteroposterior renal pelvis diameter greater than or equal to 5 mm in fetuses between 20 and 30 weeks; and a renal pelvis anteroposterior diameter greater or equal to 7 mm in fetuses between 30 and 40 weeks. Other authors used a cutoff of 4 mm to define pyelectasis.[7,9-12] In our study, the criterion used to select fetuses with pyelectasis was an anteroposterior renal pelvis diameter of 4 mm or more.

Material and methods

In contrast to most published series, our patients came from a homogeneous base low-risk population from our practice, which serves the needs of a group of about 30 obstetricians. Patients referred by physicians outside our ultrasound practice were not included in the study because they were more likely to have been referred for a suspected anomaly and, therefore, may not have represented a low-risk population.

From the 16,272 midgestation patients referred to our center from January 1998 to December 2002, 12,672 patients between 16 and 23 gestational weeks were included in the study. The other patients were removed because their initial examinations do not fall within the 16 to 23 weeks frame. None of the patients had a first trimester aneuploidy screening.

All patients underwent a thorough ultrasound examination which, aside from the AIUM-ACR guidelines, sought as many soft markers as possible, including nuchal thickening, pyelectasis, echogenic intracardiac foci, brachymesophalangia of the fifth digit, as well as a simian crease, whenever possible, for these more subtle markers were only looked at for a few seconds and, if not seen, simply passed over. In only a small percentage of fetuses did we identify this sign in accord with previous work.[13]

Hands, feet, and limb segments were included. Outflow tracts, return of pulmonary veins to the left atrium, and, when possible, both arches were also part of the routine.

Examinations were performed using either Acuson XP 128 (Siemens Medical Systems, Mountain View, Calif), Sequoia (Siemens Medical Systems), or Voluson 730 (General Electric Medical Systems, Kretztechnik, Zipf, Austria) scanners.

The results only include data from 2D examinations, not from 3D.

The aim of this study was to determine if isolated pyelectasis is a risk factor for trisomy 21. Because of the compounding risk in the presence of other markers, we analyzed the population with isolated pyelectasis and the population with other markers separately. There is a general consensus that pyelectasis is only a marker for trisomy 21 and not for other aneuploidy, and thus, our analysis only considered cases of trisomy 21. We also reported the total cases of aneuploidies recognized in the study period and the presence of pyelectasis in these cases.

The sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios with 95% CIs of pyelectasis to detect trisomy 21 were calculated. Separate analyses were conducted for fetuses with isolated pyelectasis, and for those with pyelectasis and other associated markers/structural anomalies. The following markers/structural anomalies were included: choroid plexus cysts, echogenic heart focus, 2-vessel cord, nuchal thickening, heart defects, diaphragmatic hernia, esophageal atresia, omphalocele, facial cleft, micrognathia, myelomeningocele, growth restriction, shortening of the limbs, radial aplasia, (for long bones we routinely measured humerus and femur, and we looked at ulna-radius and tibia-fibula, but only measured them if they appeared abnormal), overlapping fingers, talipes, rocker bottom feet, clinodactyly, and brachymesophalangia of the fifth digit.

Likelihood ratios were also calculated by the formula: Likelihood ratio + = sensitivity /(1− Specificity); likelihood ratio − = (1-Sensitivity)/Specificity.

The likelihood ratio expresses the odds that pyelectasis occurs in fetuses with Down syndrome versus the odds that pyelectasis occurs in fetuses without Down syndrome (Figure 1).

Follow-up information in all the cases was obtained by amniocentesis, infant postnatal reports, or by

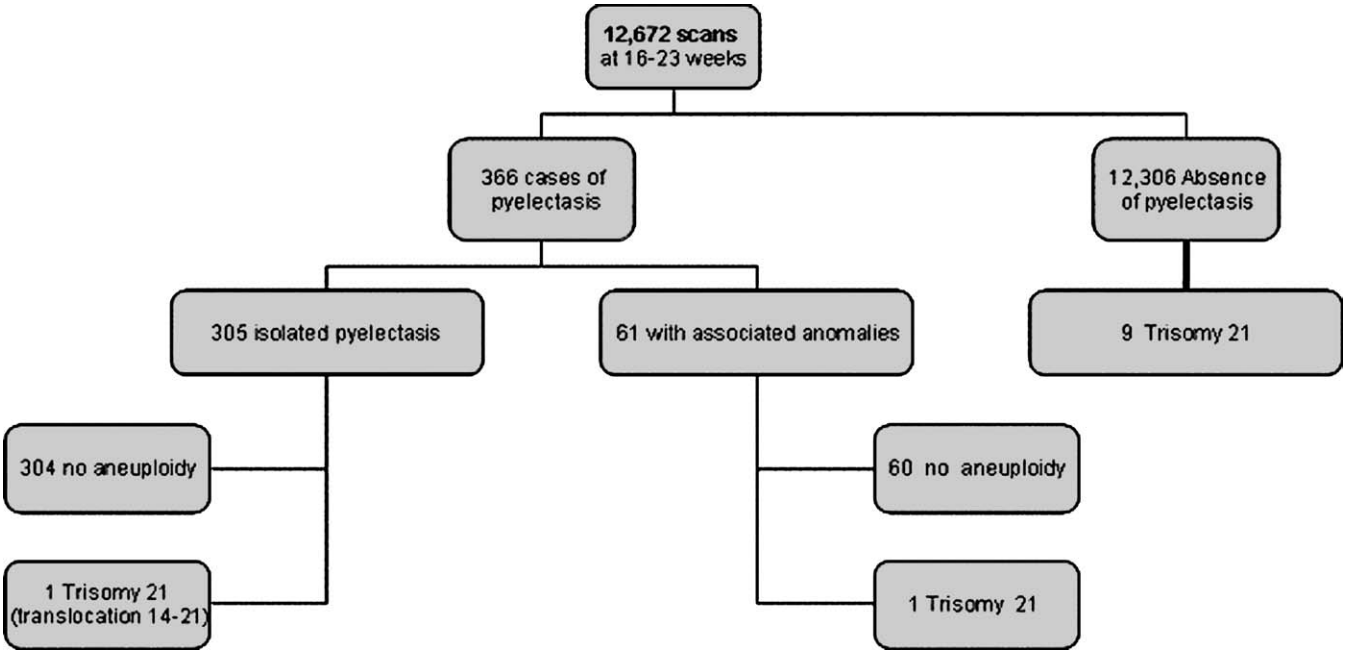

Figure 2 The distribution of pyelectasis with and without trisomy 21 in the patients examined.

Table I The prevalence, sensitivity, specificity, positive predictive value, negative predictive value, the likelihood ratio, and the diagnostic odds ratio of isolated pyelectasis to detect trisomy 21

	Total cases 12,672		
	Trisomy 21	Normal	Total
Isolated pyelectasis	1	304	305
Absence of isolated pyelectasis	10	12,357	12,367
Total	11	12,661	

Prevalence: 0.09%; sensitivity: 9.09% (95% CI 1.62–37.74); specificity: 97.6% (95% CI 97.32–97.85); PPV: 0.33%; NPV: 99.9%; +LR: 3.7862 (95% CI 0.582–24,616); −LR: 0.9315 (95% CI 0.773–1123); Diagnostic odds ratio: 4065 (95% CI 0.519–31,853).

Table II The prevalence, sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio, and diagnostic odds ratio of pyelectasis in association with other anomalies to detect trisomy 21

	Total cases 12,672		
	Trisomy 21	Normal	Total
Pyelectasis	1	60	61
Absence of pyelectasis	10	12,601	12,611
Total	11	12,661	

Prevalence: 0.09%; sensitivity: 9.09% (95% CI 1.62–37.74); specificity: 99.53% (95% CI 99.39–99.63); PPV: 1.64%; NPV: 99.92%; +LR: 19.1833 (95% CI 2.91–126.44); −LR: 0.9134 (95% CI 0.758–1.101); diagnostic odds ratio: 21,002 (CI 2647–166,637).

contacting the referring physician or pediatrician. If these options failed, the mother was interviewed. The follow-up was obtained in every case of pyelectasis.

Results

The mean maternal age was 27.2 ± (standard deviation 5.5), ranging from 15 to 42 years old. The prevalence of pyelectasis in our population was 2.9% (366/12,672). In 57% (208/366) of cases, the anteroposterior pelvis diameter measured 4 to 5 mm, in 23% (85/366) the renal pelvis measured 5 to 6 mm, in 13% (48/366) the dilatation was 6 to 7 mm, in 5% (19/366) it was 7 to 8 mm, and in 1% (4/366) the renal pelvis measured 8 mm, 1 fetus had 12 mm dilatation, and 1 had 16 mm dilatation.

The sex of the affected fetus was identified in 315 cases (in the other cases, the parents requested not to know the sex of the fetuses), with 206 (65%) fetuses being male and 109 (35%) being female. This indicated an increased prevalence of pyelectasis among males, with a male to female ratio of 1.9:1.

The prevalence of aneuploidy in the study population was 0.19% (24/12,672). Eleven fetuses had Down syndrome, including a 14-21 translocation, 6 had trisomy 18, 2 trisomy 13, and 5 had miscellaneous karyotypic anomalies including monosomy X, trisomy X, triploidy, and ring 14 chromosomes. Among cases of aneuploidy, pyelectasis was present in only 2 fetuses, both with trisomy 21: in 1 case pyelectasis was associated with other anomalies and, in the other, pyelectasis was an isolated finding.

Table III Details of the 11 cases of trisomy 21 examined in our patient population and their association with pyelectasis or other anomalies

	Karyotype	Pyelectasis	Other findings	Maternal age
1	Trisomy 21	Bilateral	Heart echogenic focus, sandal gap on the right foot	23
2	Trisomy 21	None	Heart echogenic focus, hydrocephalus, brachycephaly, hypoplasia of the fifth digit, 2-vessel cord	30
3	Trisomy 21	None	2-vessel cord	32
4	Trisomy 21	None	None	39
5	Trisomy 21	None	Omphalocele, mild ventriculomegaly, microphthalmia, micrognathia, short femur	33
6	Trisomy 21	None	Abdominal calcification	34
7	Trisomy 21	None	None	33
8	Trisomy 21	None	None	42
9	Trisomy 21	None	Echogenic heart focus	35
10	Trisomy 21	None	None	42
11	Translocation 14-21	Bilateral	None	23

In the other aneuploidy encountered (the 6 cases of trisomy 18, the 2 trisomy 13, and 5 miscellaneous karyotypic anomalies), none had pyelectasis and were considered "normal" for statistical analysis.

Table I shows the prevalence, sensitivity, specificity, positive predictive value, negative predictive value, the likelihood ratio, and the diagnostic odds ratio of isolated pyelectasis to detect trisomy 21.

Table II shows the prevalence, sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio, and diagnostic odds ratio of pyelectasis in association with other anomalies to detect trisomy 21.

Of the total patients with pyelectasis, 83.3% (305/366) were isolated cases with no other associated anomalies, which was 2.41% (305/12,672) of the total population. In one case of isolated pyelectasis with a renal pelvis dilatation of 4 mm in both kidneys, the female fetus was affected with translocation 14-21. This patient was 23 years old at the examination, 24 years old at the time of delivery, and the ultrasound was performed at 18 weeks gestation. The prevalence of trisomy 21 in the group with isolated pyelectasis was 1:305, or 0.33%. In the other patients, no other chromosomal anomalies were found.

Of the total patients with pyelectasis, 16.7% (61/366) had other associated anomalies, which was 0.48% (61/12,672) of the total population. Most of these cases were minor anomalies, such as heart echogenic focus, choroid plexus cyst, 2-vessel cords, and short humerus. Trisomy 21 was identified in a case of bilateral pyelectasis with a right dilatation of 4 mm and left dilatation of 6 mm. The other minor signs present in this fetus included a cardiac echogenic focus in the left ventricle and a sandal gap on the right foot. The prevalence of trisomy 21 in fetuses with pyelectasis and associated anomalies was 1:61, or 1.64% (Figure 2 and Table III).

In the present study, trisomy 21 was found nearly 8 times more often in association with pyelectasis (2 of 366, or 0.546%) compared with fetuses without pyelectasis (9 of 12,306, or 0.0731%).

Comment

This is one of the first large studies examining the prevalence of pyelectasis in a low-risk unselected population. We found that 2.9% of the 12,672 fetuses examined had pyelectasis: 83.3% of these were isolated cases, whereas in 16.7% other anomalies were present. Only 2 cases of pyelectasis were associated with aneuploidies (0.55%), one of which had isolated pyelectasis and Down syndrome, while the other had pyelectasis with associated anomalies and trisomy 21.

In the present study, only 1 case out of 305 fetuses with isolated pyelectasis had trisomy 21; this prevalence was higher than the expected 1 in 1100 in the general population reported from the Centers for Disease Control and Prevention.[14] However, although the likelihood ratio for fetuses trisomy 21 with isolated pyelectasis was 3.79, which appeared to be increased, if the 95% CI is calculated (0.582–24.616), the estimated risk was actually not significantly increased.

The male prevalence found in our work (male:female 1.9:1) confirmed previous reports.[15-18] Comparing our work with previous studies was rather difficult because of the various standards and parameters used. Different studies have defined pyelectasis with a range of dilatation sizes, and used populations of different compositions (high-risk, low-risk, or a mix of both). Gestational age and patient age also varied from one study to another. In some cases, authors did not differentiate between isolated pyelectasis and pyelectasis with other associated anomalies.

The prevalence of pyelectasis in our patients was 2.9%, which was similar to values calculated in other studies (see Table IV), (range between 0.72% and 2.84%). Although the true prevalence of pyelectasis in

Table IV Comparison of several studies on pylelectasis

Author	Prevalence of pyelectasis	Population	Gestational age	Cut Off	Pyelec. N	Pyelec. %
Benacerraf (8)	2.84%	7400	>16	≥4 mm between 15-20 weeks ≥5 mm between 20-30 weeks ≥7 mm between 30-40 weeks	210	2.84%
Corteville (12)	2.10%	5944	>14	≥4 mm before 33 weeks ≥7 mm after 33 weeks	127	2.14%
Nicolaides (18)	NA	Selected	15-38	≥5 mm	258	—
Wickstrom (10)	0.80%	11340	17-39	≥4 mm	82	0.72%
Wickstrom (25)	0.72%	7481	≥15	≥4 mm <33 weeks ≥7 mm >33 weeks	121	1.62%
Ouzounian et al. (28)		—	—	≥4 mm	84*	—
Chudleigh et al. (19)	0.73%	101600	16-26	≥5 mm	737	0.73%
Havutcu et al. (16)	1.25%	25586	18-24	≥5 mm	320	1.25%
Persutte et al. (15)	5.50%	5529	16-38	≥4 mm	306	5.53%
Nyberg (23)	NA	Selected	14-20	≥3 mm	186	
Rotmensch (29)	NA	Selected	14-28	≥4 mm between 15-20 weeks ≥5 mm between 20-30 weeks		
Sairam (30)	2.34%					
Current study	2.90%	12672	16-23	≥4 mm	366	2.89%

* No distintion there were among isolated and not isolated pyelectasis.
† The distinction was made only for major anomaly: 12 had concomitant anomaly: 2 T21, 1 recombinant 8 Syndrome, 3 multiple congenital anomaly, 1 IUGR, 5 fetal or infant losses.
‡ Analisys of 155 fetuses with Down syndrome.
§ Report of 187 cases of trisomy 21.

the general population was difficult to ascertain, this study provided evidence that is as close to the baseline as possible because none of the patients were preselected or referred from other centers. A summary of the previous study is provided in Table IV.

Chudleigh[19] used the percentage of pyelectasis to the number of births, not among the total ultrasound exam, and different parameter inclusions (anteroposterior diameter of the renal pelvis of 5 mm up to and including 10 mm, while we used 4 mm).

Though there was variability in the prevalence of pyelectasis in past studies (Table IV), there was a relative uniformity of result for the prevalence of trisomy 21 among fetuses with pyelectasis. Because of the small prevalence of trisomy 21, 1 or 2 cases could have strongly affected the statistical analysis in most studies.

In our study the prevalence of trisomy 21 in isolated pyelectasis was 1:305; Chudleigh[19] reported similar results (1:217, and 1:324 in women under 36 years) for isolated pyelectasis, but suggested a higher incidence for pyelectasis in association with other anomalies. In the study of Corteville,[12] among 4 cases of trisomy 21, 3 were in association with ultrasound abnormalities and, in the remaining case of trisomy 21, the abnormality was suspected. Previous studies did not find any aneuploidy for isolated fetal pyelectasis.[16] Others[20,21] concluded that the presence of pyelectasis increased the risk of aneuploidy only if it was in association with other anomalies, such as nuchal fold thickening and a short humerus.

Although Persutte et al[15] did not specify if his cases were associated with other structural anomalies or other soft signs, he found a high incidence of chromosomal anomalies (2 trisomy 21 and 1 recombinant 8 syndrome) in his 306 cases and, in addition, a high incidence of concomitant anomalies (9 cases). In the study of Nicolaides et al,[18] the suggested risk for isolated pyelectasis was an increased risk for all aneuploidy.

Different likehood ratios were reported in another study. In his "age adjusted ultrasound risk assessment" (AAURA) for Down syndrome, Nyberg[22] used a likelihood ratio for renal pyelectasis of 1.6, and in his other study,[23] an isolated pyelectasis within 14 and 20 weeks had a likelihood ratio of 1.5 (95% CI 0.6–3.6) as an

Table IV (*Continued*)

Pyelectasis		Non isolated pyelectasis		Isolated pyelectasis		Pyelec. whit other anomalies	
N	%	N	%	Normal	Anormal	Normal	Anormal
				203*	7 Trisomy 21		
—	—	—	—	—	1 Trisomy 21		6 (3 Trisomy 21; 3 Other)
163	63.18%	95	36.82%	158	1 Trisomy 21 4 other	65	30 Trisomies 21, 13, 18 other
—	—	—	—	79	3 Trisomy 21	—	—
All isolated				119	1 Trisomy 21 1 mosaic 46, XY/XYY		
						—	1 Trisomy 21
651	88.33%	98	13.30%	648	3 Trisomy 21	89	3 Trisomy 21 1 Trisomy 13 1 Trisomy 8 2 45, X0 2 Other
301	94.06%	19	5.94%	301	None	19	None
294†	96.08%	—	—	294†	None	—†	2 Trisomy 21 1 recombinant 8 Syndrome
				‡	5 Trisomy 21	‡	16 trisomy 21
				—	None	§	13 Trisomy 21
305	83.33%	61	16.67%	304	1 Traslocation 14-21	60	1 Trisomy 21

* No distintion there were among isolated and not isolated pyelectasis.

† The distinction was made only for major anomaly: 12 had concomitant anomaly: 2 T21, 1 recombinant 8 Syndrome, 3 multiple congenital anomaly, 1 IUGR, 5 fetal or infant losses.

‡ Analisys of 155 fetuses with Down syndrome.

§ Report of 187 cases of trisomy 21.

isolated finding and 5.2 overall if in combination with other markers. The reported risk was higher in the study of Whitlow[24] in the first trimester by a likelihood ratio of 8 (95% CI 2.0–31.7) for all aneuploidy and 9.6 (95% CI 1.4–64.7) for trisomy 21, although it was not clearly specified if this risk was only for isolated pyelectasis or in association with other soft markers or structural anomalies. The analysis made on 99 women by Wickstrom et al[25] indicated an increased risk for isolated fetal pyelectasis over that related to age for both Down syndrome and all chromosomal abnormalities: 3.9-fold increase in Down syndrome risk, and a 3.3-fold increase in risk for all chromosomal abnormalities.

Two different studies showed results very similar to ours among the total cases of aneuploidy and association with pyelectasis.[26,27]

Table IV summarizes the comparison with other previous study for number of population exanimate and different inclusion criteria.

Our data do not suggest an increased risk of aneuploidy for isolated pyelectasis compared with the general population.

Although the observed 3.79-fold appeared as an increase, the CIs were so large (to the point of including a decreased risk) that this study does not support an increased risk. We concluded that the recognition of an isolated pyelectasis is not an indication for amniocentesis, but an indication for a detailed exam to assess the presence of other ultrasound markers for aneuploidy. For fetuses with multiple markers (only 1 in our study, with an echogenic heart focus and a right-sided sandal gap) our likelihood ratio demonstrated an increased risk for aneuploidy.

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