Is polyhydramnios in an ultrasonographically normal fetus an indication for genetic evaluation?

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OBJECTIVE: Our purpose was to determine the frequency of fetal chromosomal anomalies in pregnancies complicated by polyhydramnios.
STUDY DESIGN: Between Jan. 1, 1992, and July 31, 1993, an amniotic fluid index was measured prospectively in 2730 third-trimester pregnant women. Polyhydramnios was defined as an amniotic fluid index ≥ 24 cm. A computer search identified all infants born with structural or chromosomal anomalies.
RESULTS: Polyhydramnios was detected in 49 of 2730 women (1.7%). The incidence of chromosomal anomalies was two in 49 (4.1%) compared with three in 2681 (0.12%) among women with normal fluid ($p < 0.05$). Six of the 49 newborns had structural anomalies (12.2%), whereas 48 of 2681 (1.8%) structural anomalies occurred in the control group ($p < 0.05$). Among study patients both fetuses with chromosomal anomalies were growth retarded; four of the six structural anomalies were associated with an amniotic fluid index > 30 cm.
CONCLUSIONS: (1) Polyhydramnios is associated with an increased incidence of congenital fetal anomalies. (2) Growth-retarded fetuses with polyhydramnios warrant genetic evaluation. (3) A genetic study is not absolutely indicated for patients with polyhydramnios and a sonographically normal fetus. (Am J Obstet Gynecol 1995;173:1523-7.)

Key words: Polyhydramnios, karyotype, structural anomalies

A pregnancy complicated by polyhydramnios presents difficult diagnostic and therapeutic dilemmas for the obstetrician. In addition, counseling a couple regarding unexplained polyhydramnios often creates significant anxiety and fosters the impression of an abnormal pregnancy. The volume of amniotic fluid varies throughout pregnancy with large daily changes regulated by complex interactions between the maternal, fetal, and placental compartments.[1, 2] Various investigators have reported that the incidence of polyhydramnios ranges from 0.2% to 1.9%.[3-5] Perinatal morbidity and mortality rates increase when polyhydramnios is present.[6] Furthermore, although an association between polyhydramnios and congenital anomalies is well documented, a wide range of results exists regarding the incidence of chromosomal abnormalities in fetuses with unexplained polyhydramnios.[4] Accordingly, the purpose of this investigation was to determine whether the presence of polyhydramnios in a sonographically normal fetus is an indication for genetic evaluation.

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Received for publication August 18, 1994; revised January 3, 1995; accepted February 14, 1995.
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0002-9378/95 $5.00 + 0 6/1/64293

Material and methods

This prospective study was conducted from Jan. 1, 1992, through July 31, 1993, at the Albert Einstein College of Medicine, Bronx, New York. A total of 2730 consecutive women with singleton pregnancies undergoing a third-trimester fetal evaluation for various obstetric indications were studied. Amniotic fluid index measurements were obtained with the use of an ATL Ultramark IX real-time scanner (ATL, Bothell, Wash.) with a 3.5 MHz linear-array transducer. With the patient typically lying in the supine position, we placed the transducer along the longitudinal axis perpendicular to the floor as described by Phelan et al.[7] The pocket of amniotic fluid with the deepest vertical dimension was identified and measured in centimeters; this procedure was repeated in each uterine quadrant and the values were summed to give the amniotic fluid index. For pockets that contained both amniotic fluid and umbilical cord, measurements of amniotic fluid index were based on the space occupied by the fluid only. We defined polyhydramnios as an amniotic fluid index ≥ 24 cm on the basis of (1) the report by Phelan et al.,[7] which found that the mean amniotic fluid index between 36 and 40 weeks' gestation was 13 ± 10 cm (±2 SDs and (2) the work of Moore and Cayle,[8] which defined normal values for the amniotic fluid index throughout gestation and determined the 97.5th percentile as > 24 cm at 37 to 41 weeks' gestation. If multiple examinations were performed on a patient,

Table I. Indications for antepartum testing

Postdates	35.3%
Diabetes	16.6%
Hypertension	13.7%
Intrauterine growth retardation	10.0%
Decreased fetal movements	4.2%
Macrosomia	3.4%
Other	17.2%

the examination with the largest amniotic fluid index was used for comparison.

In addition to measuring the amniotic fluid index, we performed a detailed ultrasonographic fetal anatomic survey. Study participants continued antepartum fetal testing in the maternal-fetal evaluation unit once or twice weekly, determined by the original indications for fetal testing. In addition, each woman was instructed to perform fetal movement counting three times daily. All women were followed up prospectively and were delivered at our institution, allowing 100% follow-up. Information on these 2730 patients evaluated during the study period in the maternal-fetal evaluation unit was entered at each visit into a computerized database system (Clicks Medical Information System, Nutley, N.J.).

Any malformation diagnosed prenatally was confirmed in the neonatal period by an attending neonatologist. Neonates with a suspicious anatomic anomaly were examined by a pediatric dysmorphologist soon after delivery. All newborn inpatient charts were reviewed after discharge to ensure that no new diagnoses of structural or chromosomal abnormalities were uncovered postnatally. The overall incidence of structural and chromosomal anomalies in live-born infants delivered at our institution during the study period was determined by a computerized review of all newborn charts.

Statistical analysis of proportional data used χ^2 analysis and Fisher's exact test. A value of $p < 0.05$ was considered significant.

Results

During the study period 5590 deliveries occurred at the Albert Einstein College of Medicine. Of these, 2730 were assessed in the maternal-fetal evaluation unit. The indications for antepartum testing are outlined in Table I. Forty-nine women (1.7%) who had at least one ultrasonographic finding of polyhydramnios comprised our study group, with the remaining 2681 women serving as a control group. Among the study group 13 cases (26.5%) were associated with maternal diabetes mellitus, of which three were pregestational. None of these diabetic women gave birth to a fetus with a structural or chromosomal anomaly. No cases of isoimmunization were found in the study population. Of the 49 patients with an amniotic fluid index of ≥24 cm, the average estimated gestational age at diagnosis was 39 weeks 1 day ± 4 days (±SD). Seventeen newborns (35%) were large for gestational age at birth, defined as >90th percentile on the Brenner curve.[9] None of these macrosomic newborns had a structural or chromosomal anomaly, and five (29.4%) were born to women with gestational diabetes. The presence of polyhydramnios was not used as an indication for intervention. There were no stillbirths in the study population.

A comparison of the incidence of fetal structural and chromosomal anomalies in 49 deliveries complicated by polyhydramnios with the 2681 women with a normal amniotic fluid index is shown in Table II. Two of the 49 patients (4.1%) demonstrated aneuploidy compared with three newborns (0.12%) in the control group ($p < 0.05$). The first patient with a chromosomal abnormality presented in the third trimester for fetal assessment because of maternal chronic hypertension. This 29-year-old woman, P0010, with a normal maternal serum α-fetoprotein level, was difficult to evaluate ultrasonographically because of maternal obesity (patient's weight was 280 pounds) and large intramural fibroids (14 × 18 cm anteriorly, 10 × 10 cm in the lower uterine segment). Although these factors resulted in a limited ultrasonographic evaluation, no anatomic abnormalities were noted. At 33 weeks' gestation the amniotic fluid index was 25 cm and the ultrasonographic estimated fetal weight was <10th percentile. The patient was delivered at 35 weeks' gestation by cesarean section because of a nonreactive nonstress test with fetal heart rate decelerations combined with the absence of end-diastolic flow on umbilical artery Doppler velocimetry. The amniotic fluid index on the day of delivery was 10 cm with membranes intact. The birth weight was 1840 gm (<10th percentile for gestational age) and the neonate was noted to have a facies suggestive of Down syndrome. No other anomalies were noted and a cardiac echo was normal. A subsequent karyotype revealed trisomy 21. The second patient, a 40-year-old woman, P5005, with three prior cesarean sections declined both maternal serum α-fetoprotein analysis and early genetic testing. This patient was seen at 33 weeks' gestation for evaluation of intrauterine growth retardation. The initial sonogram revealed a female fetus with an estimated fetal weight <10th percentile for gestational age. In addition, possible brachycephaly, hypoechoic bowel, a humerus measuring <5th percentile, and an amniotic fluid index of 25.5 cm were detected. The fetal hands were not clearly seen. The patient eventually underwent a genetic amniocentesis; however, the chromosome analysis was unavailable when the patient was delivered at 36 weeks' gestation by cesarean section for severe fetal distress. The fetal heart rate tracing revealed recurrent late decelerations, the umbilical artery flow velocimetry revealed no end-diastolic flow, and the amniotic fluid

Table II. Incidence of anomalies in pregnancies with polyhydramnios compared with control group

	Polyhydramnios	*Control group*	*Significance*
Chromosomal anomalies	2/49 (4.1%) *	3/2681 (0.12%)	$p = 0.003$
Structural anomalies	6/49 (12.2%)	48/2681 (1.8%)	$p = 0.001$

*Both infants had a birth weight < 10th percentile for gestational age.

Table III. Incidence of anomalies by amniotic fluid index

	Amniotic fluid index (cm)			
	24-25.9 (n = 22)	*26-27.9 (n = 7)*	*28-29.8 (n = 12)*	*>30 (n = 8)*
Chromosomal anomalies ($n = 2$)	2	0	0	0
Structural anomalies ($n = 6$)	0	1	1	4

index on the day of delivery was 18 cm with intact membranes. An asystolic neonate weighing 1728 gm with low-set ears, rocker-bottom feet, microglossia, and micrognathia was delivered with Apgar scores of 0 and 0 at 1 and 5 minutes, respectively. The original chromosomal study performed on the amniotic fluid eventually revealed trisomy 18.

Three of the 49 patients with polyhydramnios (6.1%) had fetal malformations limited to the genitourinary tract. All three fetuses required postnatal corrective surgery, the first for repair of a large ureterocele, the second for a unilateral ureteropelvic junction obstruction, and the third for a posterior urethral valve. Antenatally, all three fetuses demonstrated a dilated renal pelvis and hydronephrosis. In addition, three newborns were diagnosed before discharge with congenital structural anomalies, none of which were detected antenatally. One newborn had a congenital aortic valve insufficiency, another had significant cardiomegaly with biventricular hypertrophy and dorsal vertebral anomalies, and a third child had Cornelia de Lange syndrome (short stature, low-pitched cry, micrognathia, and micromelia). The incidence of major congenital anomalies in the control group was 1.8%, significantly lower than in the study group ($p < 0.05$).

Table III shows the incidence of congenital anomalies related to the degree of polyhydramnios. Four of the six fetuses with anomalies had an amniotic fluid index > 30 cm (range 30 to 41 cm).

Comment

Noninvasive means of assessing amniotic fluid volume have limitations in accuracy related to the problem of deriving a three-dimensional parameter, such as volume, from data obtained from two-dimensional ultrasonographic images. Yet numerous studies have described the ultrasonographic quantification of amniotic fluid volume by means of the amniotic fluid index and have shown it to be reproducible and proportional to the actual amniotic fluid volume.[10, 11] In addition, the amniotic fluid index has been shown by several investigators to have better sensitivity and specificity than either subjective assessment[12] or the maximum vertical pocket technique[13] in quantifying actual amniotic fluid volume.

Recognition of polyhydramnios is of benefit in identifying pregnancies at increased risk for adverse outcome. The etiology of polyhydramnios is diverse, involving both maternal and fetal disorders. The cited causes include an idiopathic origin, multiple gestation, maternal diabetes mellitus, isoimmunization, and fetal structural and chromosomal anomalies. In a recent letter to the editor Ben-Chetrit et al.[14] reported on 120 pregnancies with polyhydramnios and showed that 23 (19.2%) had fetal anomalies. A breakdown of the fetal anomalies showed gastrointestinal defects in 39%, central nervous system defects in 26%, cardiovascular defects in 22%, and urinary tract defects in the remaining 13%. However, no definition of polyhydramnios was provided by the authors.

Although polyhydramnios has been associated with structural anomalies, a broad range of results is reported regarding the frequency of specific chromosomal abnormalities. In a retrospective investigation, Landy et al.[15] discovered a 1.7% incidence of chromosomal anomalies (one in 59) among patients with idiopathic polyhydramnios. It should be noted that the definition of polyhydramnios in their study was based on the subjective observation of an experienced sonographer rather than on a more reproducible technique such as amniotic fluid index. In addition, eight of their 59 fetuses (13.6%) had structural anomalies that were undetected antenatally and that were included in the category of idiopathic polyhydramnios. Brady et al.[16] detected chromosomal anomalies by amniocentesis in four of 125 patients with polyhydramnios, for an incidence of 3.2%. All patients in their study had idiopathic hydramnios, defined as an amniotic fluid index > 24 cm, and no fetus had a structural abnormality detected by ultrasonography. However, two of the four fetuses

(both with trisomy 18) were < 10th percentile for gestational age when examined antenatally. Carlson et al.[17] reported on 49 patients referred with an amniotic fluid index ≥ 24 cm, of which six (12.2%) had chromosomal aneuploidy. However, each fetus with a chromosomal abnormality had structural anomalies noted on ultrasonography, thus excluding them from the category of idiopathic polyhydramnios. Finally, Zahn et al.[18] reported a 12% incidence of karyotypic abnormalities among 45 women with polyhydramnios to a degree requiring hospitalization. This selective population with clinically significant polyhydramnios may falsely increase the likelihood of detecting an abnormality. In addition, four of the five patients with karyotypic abnormalities had structural defects or fetal growth retardation noted ultrasonographically, thus disqualifying them from the category of idiopathic polyhydramnios. It is essential to note that none of the above studies used a control group with normal amniotic fluid volume. It is difficult therefore to ascertain whether the incidence of reported chromosomal anomalies is associated with polyhydramnios or is a function of the specific population of patients reported in each study.

We used 2681 consecutive women with a normal amniotic fluid index as our control group. In 49 patients with an amniotic fluid index > 24 cm the antenatal finding of ultrasonographically detectable polyhydramnios was associated with two trisomic infants and six structural anomalies. Although no definitive ultrasonic clues were observed in either trisomic infant, neither sonogram should be considered normal because the estimated fetal weight was < 10th percentile for gestational age. Indeed, isolated intrauterine growth retardation is particularly suggestive of a chromosomal abnormality if it is associated with polyhydramnios.[19] It should be noted that both of these trisomic fetuses, one with trisomy 18 and the other with trisomy 21, had a normal amniotic fluid index on the day of delivery. Therefore even a single examination showing polyhydramnios in a growth-retarded fetus is of concern and perhaps warrants a karyotypic analysis.

The current study represents a prospective effort to ascertain the incidence of fetal karyotypic abnormalities in fetuses with polyhydramnios in a third-trimester obstetric population. Our intent was to provide the practicing clinician with information regarding the likelihood of a chromosomal abnormality in patients with an excess of amniotic fluid. Specifically, how should an obstetrician counsel a patient with an ultrasonographic diagnosis of polyhydramnios, detected in the third trimester, yet with an anatomically normal–appearing fetus? It must be stressed that prenatal ultrasonographic screening for anomalies must be performed and interpreted by an expert sonologist. Indeed, once a diagnosis of polyhydramnios is suspected by the practicing clinician, the patient should be referred to a perinatal center with the expertise in ultrasonography for fetal anomaly detection.

It is considered standard in the United States to offer invasive cytogenetic testing to women who are 35 years old for whom the incidence of chromosomal aneuploidy at birth is approximately 0.5%. Therefore it should be demonstrated that the risk for a chromosomal aneuploidy, in women of any age, with polyhydramnios is < 1:200 to conclude that an amniocentesis is not indicated. Although none of our 49 patients with polyhydramnios and a sonographically normal fetus had a chromosomal aneuploidy, this sample size does not have enough statistical power to determine if the risk is < 1:200. Indeed, 4700 patients with polyhydramnios would be the required sample size to determine the need for genetic evaluation if the incidence of chromosomal aneuploidy was 1%, or double the risk for a woman 35 years old at a significance level of 0.05 and a power level of 0.80. Clearly, no study in the literature on excess amniotic fluid has the statistical power to justify with certainty a conclusion regarding the need for genetic evaluation in a patient with polyhydramnios.

We conclude that a finding of polyhydramnios on routine ultrasonography requires additional evaluation. Once identified, the patient with an amniotic fluid index ≥ 24 cm and a suspected fetal anomaly or growth retardation should undergo cytogenetic evaluation by means of amniocentesis, umbilical funipuncture, or placental biopsy. In addition, an incomplete or difficult ultrasonographic evaluation also mandates obtaining a fetal karyotype. However, our data indicate that when a detailed ultrasonographic examination performed by an experienced sonologist demonstrates normal anatomy, including normal fetal growth parameters, the presence of polyhydramnios alone is not an absolute indication for an invasive genetic evaluation.

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Intravaginal clindamycin treatment for bacterial vaginosis: Effects on preterm delivery and low birth weight

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OBJECTIVE: Our goal was to evaluate whether treatment of bacterial vaginosis during pregnancy with 2% clindamycin vaginal cream reduces the incidence of either preterm delivery or low birth weight or of both.

STUDY DESIGN: A multicenter, double-blind, randomized, placebo-controlled trial in Indonesia compared a 2% clindamycin vaginal cream with a placebo cream. Women seeking prenatal care at 14 to 26 weeks of gestational age who had bacterial vaginosis (Gram stain score >6 and pH of vaginal fluid >4.5) were invited to participate. Of the 745 women enrolled, 681 (91.4%) women were followed up through delivery.

RESULTS: Clindamycin vaginal cream was an effective treatment for bacterial vaginosis. Two weeks after completion of the treatment, 85.5% of the women were cured. The rate of preterm delivery (<37 weeks) was 15.0% for clindamycin patients and 13.5% for placebo patients (odds ratio 1.1, 95% confidence interval 0.7 to 1.7). The rate of low birth weight was 9.0% for clindamycin patients and 6.8% for placebo patients (odds ratio 1.3, 95% confidence interval 0.8 to 2.4).

CONCLUSIONS: Treatment of bacterial vaginosis with clindamycin vaginal cream did not reduce preterm delivery or low birth weight. Although clindamycin vaginal cream is an effective treatment for bacterial vaginosis, intravaginal treatment would not be effective against bacterial vaginosis–associated microorganisms harbored in the upper genital tract. Systemic treatment may be required to eradicate upper tract infection to reduce preterm delivery. (Am J Obstet Gynecol 1995;173:1527-31.)

Key words: Bacterial vaginosis, clindamycin, preterm delivery

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Supported by MotherCare, John Snow, Inc., through contract No. DPE-5966-Z-00-8083-00 with the United States Agency for International Development.

Received for publication August 24, 1994; revised October 31, 1994; accepted February 14, 1995.

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6/1/64294