

Outcomes From Polyhydramnios With Normal Ultrasound

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abstract

OBJECTIVE: To investigate the short- and long-term outcomes of children from pregnancies complicated with polyhydramnios, defined as amniotic fluid index (AFI) >24 cm, and with a normal detailed ultrasound examination.

METHODS: This retrospective cohort study examined 134 children aged 4 to 9 years with polyhydramnios and normal detailed ultrasound examination during pregnancy compared with 268 controls with normal AFI and normal detailed ultrasound examination matched for maternal age, year of delivery, gestational week at delivery, and presence or absence of diabetes. The primary outcome was the rate of malformations diagnosed postnatally. Additional outcomes were obstetrics outcomes, genetic syndromes, and neurodevelopment.

RESULTS: Polyhydramnios was associated with increased risk for cesarean delivery (CD) and birth weight >90th percentile. This elevation in CD was attributed to increased rate of elective CD due to suspected macrosomia. Polyhydramnios was associated with increased risk for congenital malformations ($n = 25$ [19%] compared with 27 [10%], respectively; $P = .016$) without a statistically significant increase in the rate of major malformations (11 [8%] vs. 10 [4%]; $P = .057$). Genetic syndromes were more prevalent in the polyhydramnios group (5 [3.7%] vs. 2 [0.75%]; $P = .043$), as were neurologic disorders and developmental delay (9.7% vs. 3%; $P = .004$).

CONCLUSIONS: Despite a normal detailed ultrasound examination, polyhydramnios is associated with increased rate of fetal malformations, genetic syndromes, neurologic disorders, and developmental delay, which may be diagnosed only after birth.

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Dr Yefet drafted the initial manuscript; Dr Daniel-Spiegel designed the data collection instruments and reviewed and revised the manuscript; and both authors conceptualized and designed the study and approved the final manuscript as submitted.

DOI: 10.1542/peds.2015-1948

Accepted for publication Nov 17, 2015

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

WHAT'S KNOWN ON THIS SUBJECT: The outcome of children with polyhydramnios depends on the primary etiology (eg, maternal diabetes, fetal malformations). However, the short- and long-term outcome of polyhydramnios without a prenatal known etiology with normal detailed ultrasound examination is not clear.

WHAT THIS STUDY ADDS: This study demonstrates that despite a prenatal normal detailed ultrasound examination, polyhydramnios is associated with increased risk for fetal malformations, genetic syndromes, neurologic disorders, and developmental delay that might be diagnosed only after birth.

To cite: Yefet E and Daniel-Spiegel E. Outcomes From Polyhydramnios With Normal Ultrasound. *Pediatrics*. 2016;137(2):e20151948

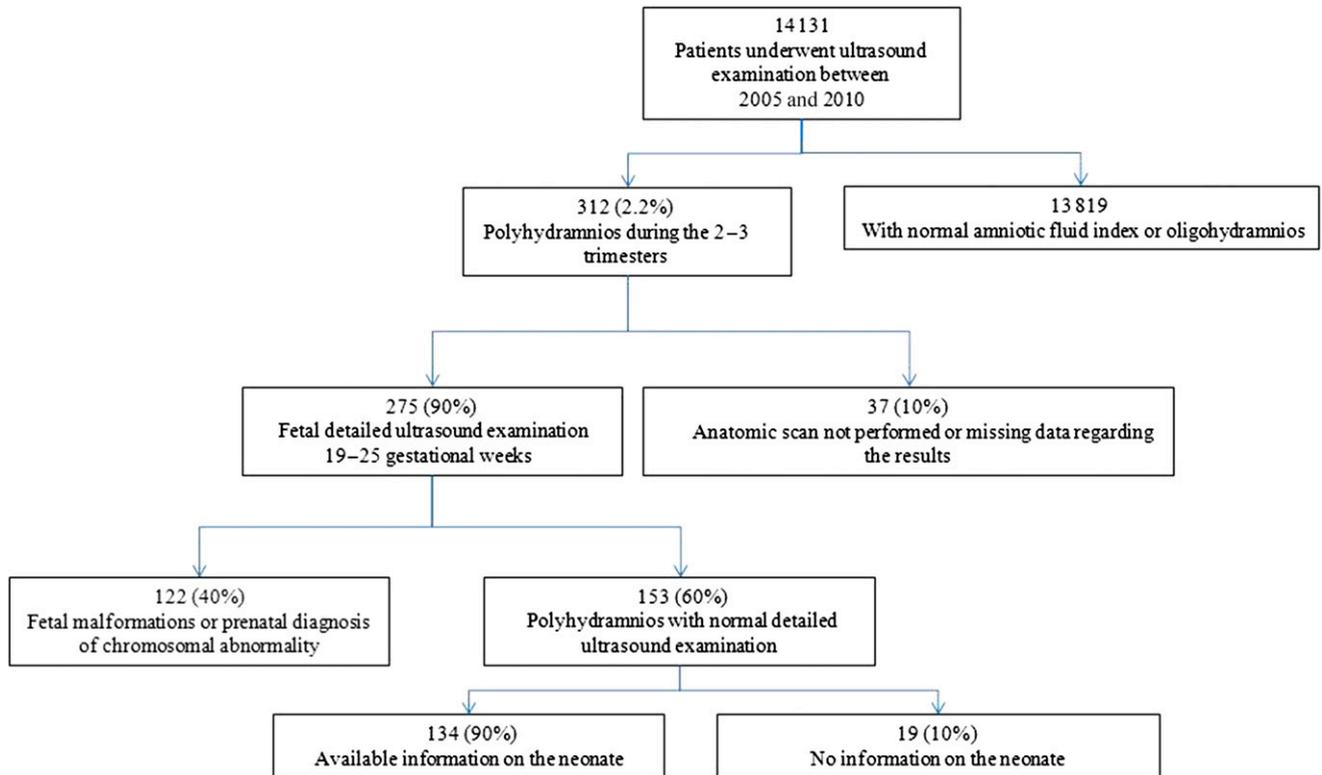


FIGURE 1
Patient flow chart.

Polyhydramnios complicates 0.5% to 2% of all pregnancies. It may be defined as either the sum of 4 quadrant measurements (amniotic fluid index [AFI]) >24 cm or a single pocket of amniotic fluid >8 cm.^{1,2} Known maternal etiologies for polyhydramnios include diabetes mellitus, placental tumors, and fetal pathologies such as fetal malformations, chromosomal aberrations, and neuromuscular abnormalities.³

Different subdivisions of polyhydramnios have been associated with different perinatal outcomes. Increasing severity correlates with increased perinatal mortality and congenital abnormalities.⁴ Early diagnosis before 30 gestational weeks has been associated with worse prognosis because of more central nervous system abnormalities.^{5,6} Persistent polyhydramnios has been associated with fetal aneuploidy,⁷ and polyhydramnios at birth has been

associated with preterm delivery, unstable lie, malpresentation,⁴ cord prolapse, and placental abruption.⁸

In 50% to 60% of cases, the etiology remains elusive during pregnancy. Polyhydramnios by itself has a prognostic implication, as pregnancies with polyhydramnios without fetal malformations are associated with increased risk for preterm labor, large for gestational age (LGA) and small for gestational age fetuses, low Apgar scores, fetal distress during labor, and increased rate of cesarean delivery (CD). Perinatal mortality was 2 to 5 times higher for neonates after pregnancies complicated with idiopathic polyhydramnios compared with the general population.^{3,9-11}

Nevertheless, data regarding the long- and short-term outcomes of children from pregnancies with polyhydramnios and normal detailed ultrasound examination is limited due to several considerations. First,

much of the data is based on studies from 20 years ago, when sonographic assessment and fetal and neonatal management were less developed. Second, other factors for unfavorable outcomes such as prematurity, which is more common in polyhydramnios, were not sufficiently controlled for. In addition, to date, the information regarding long-term outcomes of children after pregnancies with polyhydramnios is still scarce. One study that examined the effect of idiopathic polyhydramnios found abnormalities in 28.4% of cases during the first year of life;² however, the study had no control group, and some of the abnormalities were related to prematurity and not polyhydramnios per se. Studies of older children are not available. Finally, 20% of polyhydramnios cases are related to diabetes.^{3,12} Because polyhydramnios in such pregnancies is not considered idiopathic, those pregnancies were excluded from other studies and their outcome is not clear.

In the current study, we aimed to investigate the short- and long-term outcomes of children aged 4 to 9 years from pregnancies with polyhydramnios and a normal detailed ultrasound examination. We controlled for possible confounders by using a control group matched for maternal age, year of delivery, gestational week at delivery, and presence or absence of diabetes.

METHODS

Study Population

This retrospective cohort study was carried out in the obstetric department of a university teaching hospital in Afula, Israel, and included patients delivered in the hospital from 2005 to 2010. All the patients underwent a detailed ultrasound examination to evaluate fetal measurements, AFI, detailed anatomic scan, and screening for diabetes. Anatomic scans were performed as part of routine pregnancy surveillance at 19 to 25 gestational weeks according to the guidelines of the Israel Society of Ultrasound in Obstetrics and Gynecology, based on the recommendations of the American Institute of Ultrasound in Medicine.¹³ They were performed by a senior physician who is an obstetrics and gynecology specialist and who underwent additional training in ultrasound and was authorized to perform anatomic scans.

Children born during this period were 4 to 9 years old during data collection for this study.

Exclusion Criteria

Pregnancies without anatomic scans; with multiple gestation, fetal malformations, or genetic abnormalities diagnosed antenatally; with antenatal death or oligohydramnios; or in which diabetes was not evaluated were excluded from this study.

TABLE 1 Patient Characteristics

Characteristic	Polyhydramnios	Control	P
<i>n</i>	134	268	
Maternal age, y	31 ± 5.7 (31)	31 ± 5.5 (31)	.8
Maternal BMI, kg/m ²	24.4 ± 5.2 (23.4)	24.4 ± 4.8 (23.2)	.9
Gestational age at birth, wks	38.4 ± 2 (39)	38.7 ± 1.7 (39)	.1
Number of birth ^a	3 ± 1.3 (3)	3 ± 1.5 (2)	.5
Diabetes mellitus			
Gestational diabetes	21 (16)	42 (16)	1.0
Pregestational diabetes (P-GDM)	7 (5)	14 (5)	
Type 1 (% of P-GDM)	1 (14)	2 (14)	1.0
Type 2 (% of P-GDM)	6 (86)	12 (86)	
Glycemic control			
Good	17 (60)	41 (73)	
Poor	10 (34)	15 (27)	.3
Not reported	1 (4)	0	
Performed amniocentesis	35 (26)	21 (8)	0.0001
Need for amnioreduction	4 (3)	—	—
Gestational age at polyhydramnios diagnosis, wks	28.2 ± 5.6 (28)	—	—
Early: 20–29 wks 6 d	76 (57)		
Medium: 30–34 wks 6 d	36 (27)		
Late: ≥35 wks	22 (16)		
Severity of polyhydramnios ^b		—	—
Mild (AFI ≤30 cm)	93 (69)		
Severe (AFI >30 cm)	31 (23)		
Not reported	10 (8)		
Persistent polyhydramnios	97 (72)	—	—
Polyhydramnios at birth ^c		—	—
Yes	42 (31)		
No	70 (52)		
Not known	22 (17)		

Values are expressed as mean ± SD (median) or *n* (%).

^a Indicates number of births the woman had including the present one.

^b In 10 cases (8%), polyhydramnios was reported according to AFI but the value was missing.

^c In 22 cases (17%) known to have polyhydramnios, patients were diagnosed with rupture of membranes before labor when admitted to the delivery unit; therefore AFI status was not known during delivery.

Polyhydramnios Definitions

Polyhydramnios was determined by using the AFI measurement technique.¹ Color Doppler was used in cases of uncertainty regarding the presence of an umbilical cord within the measured pocket. Polyhydramnios was defined as AFI >24 cm. Repeated ultrasound for AFI evaluation was done every 4 to 6 weeks and before delivery. Additional AFI measurements were done at emergency department visits and hospitalizations. Genetic counseling followed by amniocentesis, 100-g oral glucose tolerance test, and fetal echocardiogram are recommended in these cases. Fetal echocardiogram was done in 34 patients (25% of the polyhydramnios group). Fetal echocardiogram is also indicated in patients with pregestational

diabetes; 19 of 21 patients (90%) had the examination. All the available fetal echocardiograms in this study were normal. The rest of the obstetric follow-up was the same as with normal AFI. Polyhydramnios without diabetes is not considered an indication for labor induction in our institution.

Within the polyhydramnios group, the patients were subdivided into the following groups: (1) time of diagnosis: early (20 to 29.6 gestational weeks), medium (30 to 34.6 weeks), and late (≥35 weeks); (2) severity: mild (AFI ≤30 cm) and severe (AFI >30 cm); (3) persistent polyhydramnios (defined as ≥2 sonographic examinations with polyhydramnios on different days) versus not persistent; and (4) polyhydramnios present at birth

TABLE 2 Obstetric and Short-term Outcomes

Factor	Polyhydramnios	Control	<i>p</i>
<i>n</i>	134	268	
Vacuum extraction	6 (5)	6 (2.5)	.2
CD	42 (31)	57 (21)	.02
Labor dystocia	3 (2)	5 (2)	.8
Nonreassuring fetal monitoring	3 (2.2)	10 (3.7)	.5
Elective ^a	36 (27)	42 (16)	.008
Indications for elective CD			
Previous CD	17 (13)	25 (9)	.3
Previous single CD and suspected macrosomia	4 (3)	1 (0.4)	.04
Suspected macrosomia	7 (5)	2 (0.7)	.007
Patient request	2 (1)	4 (1.5)	1
Placenta previa/tumor previa	2 (1)	1 (0.4)	.3
Malpresentation	4 (3)	9 (3)	1
Birth weight >90th percentile	27 (21)	26 (10)	.003
Birth weight <10th percentile	7 (5)	7 (2.5)	.3
Macrosomia	15 (11)	13 (5)	.02
Male newborn	70 (52)	145 (54)	.7
Nonvertex presentation ^b	4 (3)	13 (5)	.4
Meconium	13 (10)	23 (9)	.7
Perineal tear grade 3	0	0	
Apgar score <7 at 1 min	1 (0.75)	4 (1.5)	.7
Apgar score <7 at 5 min	0	1	1

Values are expressed as *n* (%).

^a Each indication for elective surgery was compared with the complete group, either polyhydramnios or control.

^b Values are different from those of the malpresentation row because the main indication was previously >1 CD in some of the cases.

versus not (in this specific analysis, cases with rupture of membranes at admission were excluded). We also collected data regarding the value of the maximal vertical pocket (MVP). In all the polyhydramnios cases according to the AFI in which the MVP measurement was available (*n* = 6), it was >8 cm, and there were no cases with MVP >8 cm in the control group.

Control Group

For each pregnancy with polyhydramnios, 2 pregnancies with normal AFI (in all the available scans) were matched according to maternal age, year of delivery, gestational week at delivery, and diabetes. Maternal age was matched using the following age groups: <20, 20 to 30, 30 to 35, 35 to 40, and >40 years. Gestational week at delivery was matched using the following ranges: ≤31 weeks (6 days) of gestation, 32 to 36 (6), 37 to 40 (6), and ≥41 (6). After defining the selection parameters, the group was chosen randomly using the random option in Excel software.

Study Outcomes

The primary outcome of this study was the rate of overall fetal malformations diagnosed postnatally in the polyhydramnios group compared with the control group. The secondary outcomes were the rates of major and minor malformations. Major malformations were considered those that generally cause functional impairment or require surgical correction.¹⁴ Additional secondary outcomes were genetic and chromosomal alterations diagnosed postnatally, obstetric outcomes such as mode of delivery, indications for CD, birth weight, gender, malpresentations, meconium, Apgar scores <7 after 1 and 5 minutes, admission to the NICU, and trauma at birth. Data regarding postnatal oxygen support, perinatal metabolic abnormalities, jaundice, need for phototherapy, and seizures were also collected.

Finally, data regarding neurodevelopment were collected. Neurodevelopment impairment

was defined as any neurologic impairment affecting motor function, emotion, learning ability, self-control, and memory that was documented in the pediatric medical record or the records of the specialized child development clinics. According to the recommendations of the Ministry of Health in Israel, all children undergo regular neurologic assessment by a pediatrician at the ages of 2 to 3 months, 9 months, 1.5 to 2 years, and 5.5 years. Additional evaluations are performed upon parent or educational staff request. Because all Israeli citizens are entitled to the same health insurance, the public health system contains all the medical data.

If the child had fetal malformations, metabolic abnormalities, or seizures as part of a genetic disease, he or she was included in the genetic diseases group and not the others.

Data Collection

Demographic and obstetric characteristics and sonographic evaluation were extracted from the electronic medical records of the ultrasound unit of the Department of Obstetrics and Gynecology at Emek Medical Center, Maternal-Fetal Medicine Unit, and Labor and Delivery Unit. Birth weight percentiles were calculated according to Dollberg growth curves, adjusted for the Israeli population.¹⁵ LGA neonates were defined as birth weight >90th percentile, and macrosomia was defined as birth weight >4000 g. Data regarding the neonates were extracted from the electronic medical records of the neonatology department and the NICU. Data regarding long-term outcomes were collected from the children's medical records in the community and from specialized child development clinics.

Statistical Analysis

Because the overall malformation rate in the general population is

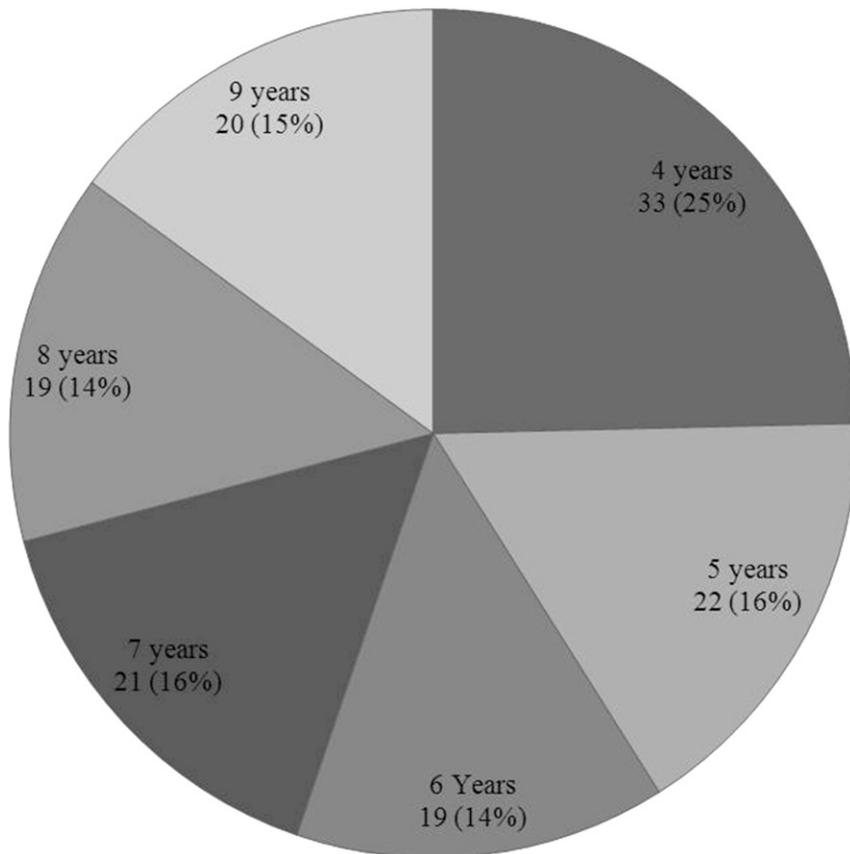


FIGURE 2
Age distribution of the children in this study from pregnancies complicated with polyhydramnios. Note that the age distribution of the children from the control group is the same.

reported to be ~5%,¹⁶ the sample size required to detect a 10% difference is 333 pregnancies in a ratio of 1:2 (111 pregnancies with polyhydramnios and 222 in the control group; 80% power, 2-sided $\alpha = 0.05$). Because 134 pregnancies matched the inclusion criteria with 268 cases in the control group, the power to detect the study hypothesis was 88%.

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as average, SD, and median. The associations between categorical variables were analyzed by using χ^2 test or Fisher exact test. For continuous data, differences were assessed with the *t* test or Mann-Whitney *U* test. Simple and multiple stepwise logistic regressions were carried out to assess interactions

between polyhydramnios and diabetes and to adjust for diabetes. Statistical analyses were carried out with SAS version 9.2 (SAS Institute, Cary, NC). Significance was set at a *P* value <.05.

The study was approved by the local institutional review board.

RESULTS

Patient Characteristics

Figure 1 shows the patient flow chart. During the study period, 14 131 women underwent an ultrasound examination in the Obstetrics and Gynecology Unit at Emek Medical Center. A total of 312 (2.2%) women had polyhydramnios during the second or third trimester. Of those, 275 women had available detailed ultrasound examination results, of

which 153 cases (60%) were normal and 134 (90%) were available for analysis.

The control group was chosen using information from the Ultrasound Unit, Maternal and Fetal Medicine Unit, and delivery unit records.

The groups' characteristics are presented in Table 1. Because in our center polyhydramnios is an indication for genetic assessment, the polyhydramnios group had more patients with amniocentesis than the control group. No cases of perinatal mortality or death later in life were reported.

Obstetric Outcomes

Table 2 summarizes the obstetric characteristics of the polyhydramnios and control groups. The risk for CD was increased in the polyhydramnios group. This was attributed to an increased rate of elective surgeries because of suspected macrosomia. Occurrence of LGA neonate and macrosomia were also significantly increased in the polyhydramnios group. The increased rates of CD, LGA, and macrosomia were also statistically significant after adjusting for diabetes (CD adjusted odds ratios [aOR] 1.745, 95% confidence interval [CI] 1.1–2.8; LGA aOR 2.5, 95% CI 1.4–4.5; macrosomia aOR 2.5, 95% CI 1.2–5.5).

The obstetric outcomes described in Table 2 were also compared according to the polyhydramnios characteristics described in Patients and Methods and Table 1. Severe polyhydramnios was associated with LGA ($n = 11$ [35%] cases in severe vs 14 [15%] in mild polyhydramnios; $P = .01$) and malpresentations (3 [10%] in severe vs 1 [1%] in mild polyhydramnios; $P = .047$). LGA was also more common when polyhydramnios was persistent compared with nonpersistent cases (25 [26%] vs 2 [6%]; $P = .01$). All the other comparisons were statistically insignificant (data not shown).

TABLE 3 Neonatal and Long-term Outcomes

Factor	Polyhydramnios	Control	<i>P</i>
<i>n</i>	134	268	
Jaundice	53 (40)	94 (35)	.4
Phototherapy	33 (25)	47 (18)	.1
Genetic disorder ^a	5 (3.7)	2 (0.75)	.04
Metabolic disorder	8 (6)	11 (4)	.4
Congenital malformation			
Overall	25 (19)	27 (10)	.02
Major ^b	11 (8)	10 (4)	.06
Minor ^b	18 (13)	23 (9)	.1
Postnatal oxygen support	2 (1.5)	5 (2)	.1
Trauma at birth	1 (0.75)	4 (1.5)	.7
Intraventricular hemorrhage	1 (0.75)	1 (0.37)	.1
Convulsions/epilepsy	0 (0)	5 (2)	.2
Neural disorders and developmental delay	13 (9.7)	8 (3)	.004
Admission to the NICU ^c	16 (12)	13 (5)	.01
Prematurity and related conditions	2 (1.5)	2 (0.7)	.6
Anemia and related conditions	3 (2.2)	2 (0.7)	.3
Respiratory problems and apnea	2 (1.5)	6 (2.2)	.7
Complications related to maternal diabetes	3 (2.2)	2 (0.7)	.3
Infections	1 (0.7)	0 (0)	.3
Congenital malformations and genetic disorders	5 (3.7)	1 (0.4)	.02

Values are expressed as *n* (%).

^a Genetic abnormalities in the polyhydramnios group were 3 children with Bartter syndrome, 1 *KCNK9* mutation, and 1 familial Mediterranean fever (FMF). In the control group, genetic abnormalities included 1 case of primary ciliary dyskinesia and 1 FMF.

^b Children with simultaneous major and minor malformations are listed in both rows.

^c Primary indication for NICU admission. Genetic disorders refer to abnormalities that were later diagnosed as part of a genetic syndrome.

Neonatal Outcomes

Figure 2 describes the age distribution of the children in this study. The children's outcomes in the polyhydramnios group compared with the control group are presented in Table 3. All the children were included in the analysis.

Fifty-six malformations were found in this study (Table 4). The most common were ventricular septal defects, isolated or with other cardiac anomalies (10 [18%] cases). Sonographic prenatal diagnosis was possible in only 35 (63%) of the cases. Findings that are not routinely diagnosed in anatomic scans are anatomic defects visible only after birth (eg, patent ductus arteriosus), soft anatomic changes (eg, ankyloglossia), and defects that are predominantly functional in nature. The average time for postnatal malformation diagnosis was 7.4 ± 15.6 months.

The overall malformation rate in the polyhydramnios group was almost

twice that of the control group. No specific system was found to be more affected than others (Table 5). The risk was also statistically significant after adjusting for diabetes (aOR 2.1, 95% CI 1.2–3.8). Characteristics of polyhydramnios severity, time of diagnosis, and persistence did not modify the risk (data not shown).

The risk for genetic diseases was increased in the polyhydramnios group compared with the control group. The risk for genetic abnormalities was more pronounced in the severe polyhydramnios group than in the mild cases (3 [9.7%] vs 2 [2.15%], respectively; *P* = .008). The risk for genetic malformations in the mild polyhydramnios cases was not statistically different from that of the control group (2 [2.15%] vs 2 [0.75%]; *P* = .2). Other polyhydramnios characteristics did not modify the risk (data not shown).

More children were admitted to the NICU in the polyhydramnios group

TABLE 4 Diagnosed Malformations and Prevalence

Malformation	<i>n</i>
Umbilical hernia	6
Ventricular septal defect	5
Ventricular septal defect with other cardiac malformation	5
Valvular stenosis or insufficiency	3
Congenital hearing loss	3
External hydrocephalus	2
Congenital hip dysplasia and torticollis	2
Varicocele and hydrocele of spermatic cord	2
Hydronephrosis	2
Hypospadias	2
Vesicoureteral reflux	2
Metatarsus varus	1
Atrial septal defect	1
Atrial septal defect and pulmonary valve stenosis	1
Branchial cleft cyst	1
Congenital anal fissure	1
Congenital dislocation of hip	1
Congenital hypothyroidism	1
Congenital talipes valgus	1
Hypertrophic cardiomyopathy	1
Congenital laryngomalacia	1
Micropenis	1
Congenital deformity of hip joint	1
Brown syndrome (congenital)	1
Patent ductus arteriosus	1
Patent foramen ovale and patent ductus arteriosus	1
Patent foramen ovale and peripheral pulmonary stenosis	1
Pharyngeal anomaly	1
Polydactyly	1
Pyloric stenosis	1
Rectal prolapse	1
Ankyloglossia	1
Congenital torticollis	1

(Table 3), also after adjusting for diabetes (aOR 2.7, 95% CI 1.3–6). This difference was attributed to genetic problems and congenital malformations (Table 3).

Long-Term Neurodevelopment

The polyhydramnios group demonstrated an increased rate of neurodevelopment problems compared with the control group (Table 3). The types of neurodevelopment disorders are listed in Table 6. The increased rate was still statistically significant after controlling for diabetes (aOR 3.5, 95% CI 1.4–8.7). No association was demonstrated between

TABLE 5 Overall Congenital Malformations by Organ System^a

System	Polyhydramnios	Control	<i>P</i>
<i>n</i>	134	268	
Cardiovascular	10 (7.5)	9 (3.4)	.07
Genitourinary	5 (3.7)	4 (2.2)	.2
Skeletal	5 (3.7)	6 (2.2)	.5
Abdominal wall defect	3 (2.2)	3 (1.1)	.4
Congenital hypothyroidism	0 (0)	1 (0.37)	1
Gastrointestinal	1 (0.75)	3 (1.1)	1
Respiratory	2 (1.5)	0 (0)	.1
Central nervous system	1 (0.75)	3 (1.1)	1

Values are expressed as *n* (%).

^a Children who had malformations in >1 system are listed in all the relevant rows.

TABLE 6 Types of Neurodevelopmental Disorders

Type of Disorder	Polyhydramnios	Control	<i>P</i>
<i>n</i>	134	268	
Motoric difficulties and general slow development	8 (6)	3 (1.1)	.008
Speech disturbance	3 (3.7)	1 (0.37)	.1
Attention and learning disorders	5 (3.7)	2 (0.75)	.04
Pervasive developmental disorder	0 (0)	2 (0.75)	.5

neurodevelopment impairment and fetal malformations (OR 1.6, 95% CI 0.5–5.1). Polyhydramnios characteristics did not modify the risk (data not shown).

Diabetes Subanalysis

We performed a separate analysis of the short- and long-term outcomes of diabetic patients with and without polyhydramnios (Table 7). When polyhydramnios was present, the risk for CD was elevated, particularly in cases of previous CD with suspected macrosomia. There were also more cases of NICU admissions and congenital malformations (Table 7). When we used multiple logistic regression to examine whether diabetes modified the effect of polyhydramnios on short- and long-term outcomes, the interaction terms were statistically insignificant ($P > .05$), suggesting that diabetes did not modify the effect of polyhydramnios on the study outcomes.

DISCUSSION

In the current study, we investigated the long- and short-term outcomes

of children after pregnancies with polyhydramnios. Approximately 2% of the pregnancies were diagnosed with polyhydramnios, and 60% of those were considered idiopathic. These results are consistent with previous studies.³

The results demonstrated that polyhydramnios increased the risk for CD, LGA, and macrosomia. This information was reported previously.^{4,17–21} This study is innovative in demonstrating that the rate of CD was increased mainly due to elective surgeries for suspected macrosomia and not emergent CD during labor. Macrosomia has previously been shown to be a risk factor for CD.^{22,23} Thus, one might suggest that those cases would be operated on anyway if allowed to undergo a trial of labor. However, this is not necessarily the case, as suspected macrosomia before labor (either true or false) increased the risk for CD.^{24,25}

In the current study, it was shown that although all the children underwent documented normal sonographic anatomic scan during pregnancy, in the polyhydramnios

group, the overall rate of malformations diagnosed postnatally was higher than that of the general population. The risk for congenital malformations varies between studies, ranging from 2% to 6%, and depends on the population investigated and the definition used.¹⁴ In this study, the incidence of fetal malformations in the control group was 10%, which is higher than previously reported.^{16,26,27} The risk for major anomaly in the presence of polyhydramnios and normal detailed sonographic examination was also higher than previously reported by Dashe et al.²⁸ A possible explanation is that studies of congenital malformations are based on records from the perinatal and neonatal periods, whereas we also considered malformations diagnosed years after birth. The most common malformations in our study were of the cardiovascular system. This is consistent with the results of Dashe et al.²⁸ In their cohort, the antenatal detection rate of cardiac anomalies was the lowest and reached only 40%.²⁸

Polyhydramnios also increased the risk for genetic disorders, especially in the severe cases. It should be noted that during the study period, genetic assessment included only fetal karyotype. Now that comparative genomic hybridization has been introduced, the association of idiopathic polyhydramnios with genetic abnormalities should be reassessed in future studies.

In this study, there were 3 cases of Bartter syndrome. This syndrome is caused by mutations of genes encoding proteins of the ion channels in the thick ascending limb of the nephron.²⁹ Severe polyhydramnios is caused by excessive fetal urination. In our area, there are several families known to carry Bartter syndrome mutations. Similarly, the risk for genetic

TABLE 7 Subanalysis of Study Outcomes in Pregnancies With Diabetes, With and Without Polyhydramnios

Factor	Polyhydramnios	Control	P
<i>n</i>	28	56	
Vacuum extraction	1 (3.6)	0 (0)	.3
CD	15 (54)	17 (30)	.04
Labor dystocia	0 (0)	2 (3.6)	.6
Nonreassuring fetal monitoring	3 (11)	2 (3.6)	.3
Elective ^a	12 (43)	13 (23)	.06
Previous CD	5 (18)	6 (11)	.5
Previous single CD and suspected macrosomia	3 (11)	0 (0)	.03
Suspected macrosomia	3 (11)	2 (3.6)	.3
Patient request	1 (3.6)	3 (5.4)	1
Placenta previa/tumor previa	0 (0)	0 (0)	1
Malpresentation	0 (0)	2 (3.6)	1
Birth weight >90th percentile	8 (28)	8 (14)	.1
Birth weight <10th percentile	2 (7.2)	2 (3.6)	.6
Macrosomia	5 (18)	4 (7.1)	.2
Male newborn	16 (57)	29 (52)	.6
Nonvertex presentation	0 (0)	2 (3.6)	.6
Meconium	0 (0)	5 (9)	.2
Perineal tear grade 3	0 (0)	0 (0)	1
Apgar score <7 at 1 min	0 (0)	1 (1.8)	1
Apgar score <7 at 5 min	0 (0)	0 (0)	1
Admission to the NICU	5 (18)	2 (3.6)	.04
Jaundice	15 (54)	20 (36)	.1
Phototherapy	10 (36)	11 (20)	.1
Genetic disorder	1 (3.6)	0 (0)	.3
Metabolic disorder	6 (21)	5 (9)	.2
Congenital malformations (overall)	10 (35)	6 (11)	.006
Postnatal oxygen support	1 (3.6)	0 (0)	.3
Trauma at birth	0 (0)	0 (0)	1
Intraventricular hemorrhage	0 (0)	0 (0)	1
Convulsions/epilepsy	0 (0)	2 (3.6)	.6
Neural disorders and developmental delay	3 (11)	2 (3.6)	.3

Values are expressed as *n* (%).

^a Each indication for elective surgery was compared with the whole group, either polyhydramnios or control.

mutations probably depends on the prevalence of genetic diseases associated with polyhydramnios in specific populations.

This study found an increased risk for neurodevelopmental delay and learning problems. To our knowledge, this is the first study to report on this outcome and in school-aged children. The association between polyhydramnios and neurodevelopmental delay is not clear. A possible hypothesis is that the swallowing mechanism, which is representative of normal neurologic function in utero, is less developed in those fetuses, resulting in the formation of polyhydramnios. However, this result as well as the hypothesis should be investigated

further, including in larger prospective studies.

In this study, we included pregnancies with diabetes. We chose to do so because although this group makes up 20% of the cases of polyhydramnios, the information in the literature regarding such pregnancies with a normal anatomic scan is scarce. Moreover, because polyhydramnios is a marker for uncontrolled diabetes, the patients with diabetes in the polyhydramnios and control groups might act differently because of the nature of glycemic control and not because of polyhydramnios per se. We showed that the risks for CD, admission to the NICU, and congenital malformations were elevated in the presence of polyhydramnios. Other outcomes

were not statistically significant between the groups; however, this might be attributed to the small sample size of pregnancies with diabetes. Interestingly, the risk for unfavorable outcomes in polyhydramnios was not modified by the presence of diabetes.

The strengths of this study are the use of single-hospital information and electronic documentations that were made in real time. The control group was chosen randomly by computer from all births in the appropriate years, thus minimizing selection bias. Using a control group matched for possible confounders for unfavorable outcomes such as maternal age and gestational week enables isolation of the net effect of polyhydramnios on the study outcomes.

The limitations of this study are those inherent to the use of retrospective databases. However, inaccuracies were minimized by the use of multiple sources such as hospitalization records and documents from the ultrasound unit, pediatrics department, pediatricians, and child development clinics. Another limitation is the fact that long-term diagnosis might be influenced by the parents' awareness and compliance with medical surveillance. Because the maternal characteristics were similar in the polyhydramnios and control groups, and because according to the law in Israel all citizens are entitled to the same health insurance, the difference in medical availability and accessibility should not be substantially different between the groups. A regular screening program for neurodevelopment in schools and kindergartens also helps to minimize possible differences. It is acknowledged that subgroup analyses in this study are underpowered, and therefore their results should be interpreted with caution.

CONCLUSIONS

In summary, this study demonstrates that even after controlling for possible confounders including diabetes, pregnancies complicated with polyhydramnios after normal detailed ultrasound examination are at increased risk for CD, fetal macrosomia, congenital malformation, and genetic abnormalities, as well as neurodevelopment abnormalities and delay. This information should be discussed with the patient, and children should be closely overseen by pediatricians and child development clinics. Finally, this important topic should be investigated further, particularly in prospective studies designed to overcome the limitations of the current study.

ACKNOWLEDGMENTS

We thank Naama Schwartz, PhD for her kind assistance in the statistical analysis. We also thank Mrs Snaith Ayalon for her assistance in data mining.

ABBREVIATIONS

AFI: amniotic fluid index
aOR: adjusted odds ratio
CD: cesarean delivery
CI: confidence interval
LGA: large for gestational age
MVP: maximal vertical pocket

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Pediatrics 2016;137;

DOI: 10.1542/peds.2015-1948 originally published online January 11, 2016;

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