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MATERNAL-FETAL MEDICINE

The association between pregnancies complicated with isolated polyhydramnios or oligohydramnios and offspring long-term gastrointestinal morbidity

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Abstract

Objective Infants born to mothers with pregnancies complicated by polyhydramnios or oligohydramnios are at an increased risk for significant adverse perinatal outcome. We sought to assess whether in utero exposure to amniotic fluid abnormalities increases the risk of long-term gastrointestinal (GI) morbidity in the offspring.

Methods In a population-based cohort study, the incidence of GI-related hospitalizations was compared between singletons exposed and unexposed to oligohydramnios or polyhydramnios. Deliveries occurred between the years 1991–2014 in a regional tertiary medical center. Offspring GI morbidity was assessed up to the age of 18 years according to a pre-defined set of International Classification ofDiseases, ninth revision (ICD-9) codes associated with hospitalization. A Kaplan–Meier survival curve was used to compare cumulative morbidity incidence. A Cox proportional hazard model was performed to control for confounders.

Results During the study period, 186,196 newborns met the inclusion criteria, of which 2.1% ($n=4063$) and 3.0% ($n=5684$) were born following pregnancies with oligohydramnios and polyhydramnios, respectively. The Kaplan–Meier curve demonstrated that children exposed to isolated oligohydramnios (but not to polyhydramnios) had higher cumulative incidence of GI morbidity (log-rank test, $p=0.001$). In the Cox regression model, controlled for maternal age, gestational age, birth weight, and mode of delivery, isolated oligohydramnios (adjusted HR 1.2, 95% CI 1.04–1.34, $p=0.007$), but not polyhydramnios (adjusted HR 1.1, 95% CI 0.91–1.13, $p=0.766$), was found to be independently associated with long-term GI morbidity of the offspring.

Conclusion In utero exposure to isolated oligohydramnios is an independent risk factor for long-term GI morbidity in the offspring.

Keywords Long-term morbidities · Pediatric gastrointestinal morbidity · Pediatric gastrointestinal health outcomes · Polyhydramnios · Oligohydramnios

Introduction

Amniotic fluid plays a significant role in the normal development of the fetus during pregnancy, and in the delivery process itself, with definite implications on offspring future health [1, 2]. The most common techniques used for ultrasound measurement of amniotic fluid amount include maximal vertical

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pocket (MVP) or amniotic fluid index (AFI) [3]. MVP refers to the vertical dimension (in cm) of the largest pocket of amniotic fluid not persistently containing umbilical cord or fetal extremities. AFI is calculated by dividing the uterus into four quadrants. The four maximal vertical amniotic fluid pocket diameters are summed for the final index [3, 4]. Polyhydramnios is defined as an abnormally large volume of amniotic fluid for a given gestational age and may be idiopathic or associated with a variety of fetal or maternal disorders. Among the most common maternal-related factors are gestational and pre-gestational diabetes mellitus, and in utero viral infections [5]. Polyhydramnios has also been associated with fetal central nervous system (CNS) defects, GI obstruction and impaired fetal swallowing, and other fetal malformations [6]. Polyhydramnios, typically if mild or present during the third trimester, is commonly idiopathic [7]. The current literature focuses on the short-term outcomes of polyhydramnios, including placental abruption, abnormal presentation, umbilical cord prolapse, and preterm delivery [8, 9].

Oligohydramnios is defined as low amniotic fluid volume for a given gestational age [10]. Oligohydramnios etiologies vary according to gestational age upon diagnosis and severity [11]. The majority of women with oligohydramnios or borderline amniotic fluid volume have no identifiable cause [12]. Common conditions associated with oligohydramnios include fetal genitourinary malformations [13, 14] and placental insufficiency [15]. Oligohydramnios in itself, regardless of the etiology, can impair fetal development and in extreme conditions may result in malformations, umbilical cord compression, and perinatal death [16]. Short-term outcomes associated with oligohydramnios include increased rates of cesarean deliveries (CD), fetal distress, and small for gestational age (SGA) birth weights [17].

As previously noted, an association between amniotic fluid abnormalities and fetal GI malformations was demonstrated [6]; nevertheless, little is known regarding long-term outcome of offspring born following pregnancies complicated with isolated polyhydramnios or oligohydramnios [18]. Furthermore, to the best of our knowledge, no study has examined the long-term GI outcomes of the offspring in pregnancies with isolated amniotic fluid abnormalities.

We thus aimed to examine the association between pregnancies complicated with isolated polyhydramnios and oligohydramnios and offspring long-term GI morbidities in a large cohort of children followed up to the age of 18 years.

Materials and methods

Setting

The study was conducted at the Soroka University Medical Center (SUMC), the sole tertiary hospital in Israel's southern region, serving the entire population of the area.

Study population

The study population included all singleton deliveries of mothers occurring during the years 1991–2014. Patients lacking parental care, perinatal death cases, and offspring with congenital malformations (including urogenital/renal malformations) or chromosomal abnormalities were excluded from the study. To restrict the study to isolated cases of oligohydramnios and polyhydramnios, the following groups were also excluded from the initial analysis: hypertensive disorders during pregnancy (including cases of chronic hypertension, gestational hypertension and preeclampsia, $n = 12{,}247$) intra-uterine growth restriction ($n = 4487$), deliveries with placental abruption ($n = 1359$), deliveries with premature rupture of membranes ($n = 21{,}001$), maternal diabetes mellitus (pre-gestational and gestational, $n = 12{,}159$) and cases of RH isoimmunization ($n = 56$).

Study design

We conducted a population-based cohort study. Exposure was defined as pregnancy complicated with either isolated polyhydramnios or oligohydramnios. Polyhydramnios was defined as an abnormally high volume of amniotic fluid for a given gestational age, defined as MVP > 8 cm, or AFI > 24 cm. Oligohydramnios was defined as an abnormally low volume of amniotic fluid for a given gestational age, defined as MVP < 2 cm, or AFI < 5 cm [3, 4]. The comparison group consisted of pregnancies with normal amniotic fluid measurements. The main outcome was defined as long-term GI-related hospitalizations of the offspring, as documented in the hospital computerized files. GI morbidity included a pre-defined set of International Classification of Diseases, ninth revision codes (ICD-9) as detailed in the supplementary table. Main GI morbidity categories included anatomic-structural malformations (e.g., hernias, abdominal wall defects), esophageal diseases, gastroduodenal diseases, colonic diseases, inflammatory bowel diseases (IBD), vascular (hemorrhoids), and celiac.

Our database was created from two different databases that were cross-linked and merged: the computerized perinatal database and the computerized pediatric

hospitalization database of SUMC. The perinatal database consists of information recorded directly after delivery by an obstetrician. The hospitalization database includes demographic information and ICD-9 codes for all medical diagnoses made during hospitalization.

The study was approved by the local ethical committee, according to the declaration of Helsinki (REB number-SOR-0438-15) (Fig. 1).

Statistical analysis

Statistical analysis was performed with SPSS software (Version 23; IBM Corp, Armonk, NY, USA). ANOVA and χ^2 tests were used to compare background characteristics and outcomes between the three study groups. A Kaplan–Meier survival curve was used to compare cumulative incidence of GI morbidity. Cox proportional hazard model analysis was used to control for confounders, using two dummy variables which compared polyhydramnios and oligohydramnios to control pregnancies. A probability of alpha error was set at < 0.05.

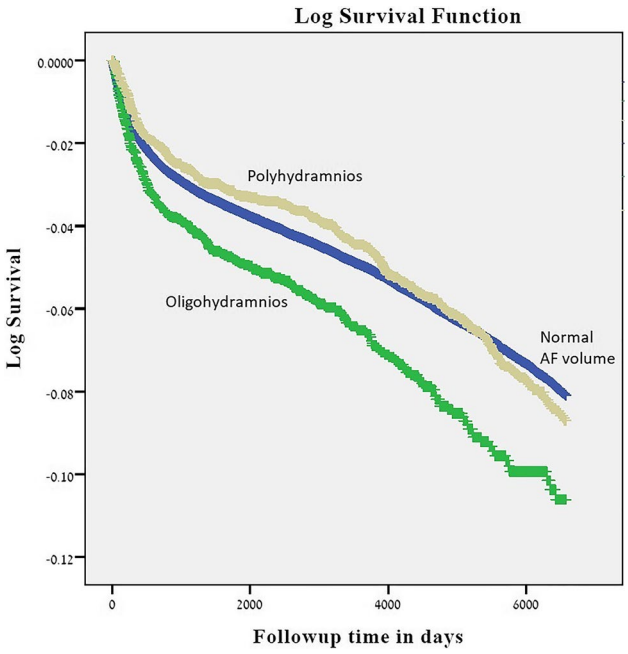

Fig. 1 Kaplan–Meier survival curve demonstrating the cumulative incidence of GI hospitalizations according to prenatal oligohydramnios or polyhydramnios exposure (log-rank test $p = 0.001$)

Results

During the study period, 195,943 deliveries met the inclusion criteria, 2.9% ($n = 5684$) of which were complicated with polyhydramnios and 2.1% ($n = 4063$) of which were complicated with oligohydramnios.

Table 1 presents the clinical characteristics of the study population. Mothers with polyhydramnios were older on average and with a higher mean parity. Rates of obesity were significantly higher among mothers with polyhydramnios and oligohydramnios as compared with mothers with normal AFI. Rates of small for gestational age (SGA) newborns, defined when the birth weight is below the 5th percentile for gestational age, were significantly higher among pregnancies with oligohydramnios, while rates of macrosomia, birth weight that is higher than 4000 g, were significantly higher among pregnancies with polyhydramnios. Mothers with polyhydramnios or oligohydramnios underwent cesarean deliveries more often (CD; 21.7%, 18.7% and 10.9% for polyhydramnios, oligohydramnios and normal amniotic fluid levels, respectively, p value < 0.001).

Table 2 presents the long-term GI morbidity of offspring within the study groups, comparing each group of children exposed in utero to polyhydramnios, and to oligohydramnios, to the comparison group consisted of pregnancies with normal amniotic fluid measurements.

During the follow-up period, children exposed in utero to isolated amniotic fluid disorders had significantly higher rates of total GI-related hospitalizations (6.1%, 6.6% and 5.1% for polyhydramnios, oligohydramnios and normal amniotic fluid levels, respectively, p value < 0.001). However, in the Kaplan–Meier survival curve only children exposed in utero to oligohydramnios, (and not to polyhydramnios) exhibited higher cumulative incidence of GI morbidity as compared with their unexposed counterparts (log-rank test $p < 0.001$).

Table 3 presents a cox multivariable regression model which controlled for various clinically relevant confounders including maternal age, gestational age, labor induction, mode of delivery, and birth weight. Oligohydramnios was found to be independently associated with long-term GI morbidity of the offspring with an adjusted hazard ratio of 1.2 (95% CI 1.04–1.34, p value $= 0.007$).

Discussion

In this large population-based cohort study with a long follow-up period, we found that children who were exposed in utero to isolated oligohydramnios were at a significantly

Table 1 Cohort characteristics by exposure to oligohydramnios or polyhydramnios

Characteristics	No oligohydramnios or polyhydramnios $n=186,196$ (95%)	Oligohydramnios $n=4063$ (2.1%)	Polyhydramnios $n=5684$ (2.9%)	p value*
Maternal age, years, (mean ± SD)	27.8 ± 5.6	27.8 ± 5.6	29.1 ± 5.8	< 0.001
Gestational age, weeks, (mean ± SD)	39.3 ± 1.6	39.5 ± 1.7	39.3 ± 1.7	< 0.001
Gravity				< 0.001
1	33,482 (18.0)	1199 (29.5)	724 (12.7)	
2–4	92,299 (49.6)	1794 (44.2)	2720 (47.9)	
5 +	60,394 (32.4)	1070 (26.3)	2239 (39.4)	
Parity				< 0.001
1	39,778 (21.4)	1471 (36.2)	884 (15.6)	
2–4	98,969 (53.2)	1802 (44.4)	3036 (53.4)	
5 +	47,426 (25.5)	788 (19.4)	1763 (31.0)	
Obesity	1705 (0.9)	50 (1.2)	161 (2.8)	< 0.001
Placenta previa	672 (0.4)	12 (0.3)	19 (0.3)	0.750
Preterm delivery	8758 (4.7)	202 (5.0)	320 (5.6)	0.004
Labor induction	39,428 (21.2)	2528 (62.2)	1739 (30.6)	< 0.001
Cesarean delivery	20,379 (10.9)	759 (18.7)	1233 (21.7)	< 0.001
Gender of offspring				< 0.001
Male	94,340 (50.7)	2091 (51.5)	3185 (56.0)	
Female	91,856 (49.3)	1972 (48.5)	2499 (44.0)	
Gestational weight	3240.9 ± 451.0	3107.9 ± 462.1	3439.0 ± 494.1	< 0.001
< 2500 g	7815 (4.2)	293 (7.2)	171 (3.0)	
2500–3999 g	169,885 (91.2)	3655 (90.0)	4833 (85.0)	
> 4000 g	8495 (4.6)	115 (2.8)	680 (12.0)	
Macrosomia	8242 (4.4)	105 (2.6)	668 (11.8)	< 0.001
SGA	6962 (3.7)	358 (8.8)	97 (1.7)	< 0.001
Apgar score < 7 at 1 min	8536 (4.6)	202 (5.0)	332 (5.8)	< 0.001
Apgar score < 7 at 5 min	3816 (2.0)	28 (0.7)	51 (0.9)	< 0.001

Table 2 Incidence rate for disease-specific hospitalizations

Gastrointestinal morbidity	No oligohydramnios or polyhydramnios $n=186,195$ (95%)	Oligohydramnios $n=4063$ (2.1%)	Polyhydramnios $n=5684$ (2.9%)	p value*
Esophageal disease	375 (0.2)	16 (0.4)	8 (0.1)	0.015
Gastroduodenal disease	964 (0.5%)	31 (0.8%)	31 (0.5%)	0.098
Appendix disease	1101 (0.6%)	21 (0.5%)	60 (1.1%)	< 0.001
Hernia (inguinal umbilical abdominal wall)	2483 (1.3%)	68 (1.7%)	73 (1.3%)	0.164
IBD	3048 (1.6%)	82 (2.0%)	102 (1.8%)	0.115
Colonic-functional disease	278 (0.1%)	9 (0.2%)	17 (0.3%)	0.01
Anorectal disease	364 (0.2%)	10 (0.2%)	18 (0.3%)	0.106
Surgical obstruction	229 (0.1%)	10 (0.2%)	6 (0.1)	0.82
Celiac	684 (0.4%)	22 (0.5%)	29 (0.5%)	0.48
Hemorrhoids	194 (0.1%)	3 (0.1%)	8 (0.1%)	0.582
Total GI hospitalization	9557 (5.1%)	268 (6.6%)	346 (6.1%)	< 0.001

increased risk for long-term GI morbidity independent of many relevant obstetrical factors. Isolated polyhydramnios was not found to carry a similar risk. To the best of our knowledge, the association between abnormal amount of amniotic fluid in pregnancy and long-term GI morbidities has not been previously reported.

Table 3 Cox multivariable regression models for the risk of gastrointestinal-related hospitalization of the offspring

	Adjusted HR	95% CI 95%	*p* value
Oligohydramnios	1.18	1.04–1.34	0.007
Polyhydramnios	1.01	0.91–1.13	0.766
Preterm delivery	1.24	1.14–1.35	< 0.001
Birth weight (g)	1.00	1.00–1.00	< 0.001
Maternal age (years)	0.99	0.98–0.99	< 0.001
Cesarean delivery	1.27	1.19–1.34	< 0.001
Labor induction	1.18	1.13–1.23	< 0.001

An association between other adverse pregnancy outcomes, such as SGA, and long-term GI morbidity was previously suggested by our group and by others [19, 20]. A possible underlying mechanism for this observation involves an impaired intra-uterine environment. A hostile intra-uterine environment (i.e., placental insufficiency), leading to oligohydramnios or fetal growth restriction, may affect fetal gut development and its immune system.

The notion of prenatal programing suggests that intrauterine exposures have a long-lasting effect on offspring health. Accordingly, early microbial colonization process beginning in utero may have a long-lasting influence on the risk of GI disease, allergic, autoimmune and metabolic disease [21]. In our study, we found children exposed to isolated oligohydramnios in utero, to be at a significantly higher risk of GI-related morbidity. Potentially, different patterns of microbiome, typical of different amniotic fluid volumes, may lead to different fetal gut colonization. Lee et al. found that oligohydramnios was more prevalent in patients with culture-proven amniotic fluid infection than in those with intra-amniotic inflammation and negative amniotic fluid culture [22]. This may support the hypothesis that oligohydramnios and polyhydramnios differ in microbiome, with different predispositions for amniotic fluid infection.

Another explanation for our findings can be related to delivery mode. High rates of cesarean deliveries were noted in both groups of amniotic fluid abnormalities and mode of delivery has a definite role in microbial colonization of the child's GI system [23, 24].

Short-term perinatal outcomes seen in our study among the oligohydramnios group include higher rates of SGA (8.8% compared to 3.7% among normal AFI) and lower mean Apgar scores. These adverse outcomes may result from various conditions un-diagnosed -during the pregnancy which may also be responsible for higher rates of later childhood GI morbidity of the offspring. Nevertheless, we adjusted for many obstetrical factors in the Cox regression model, yet the association appeared stable and independent.

Our study's main strengths are the large-scale cohort, as well as the population-based nature of data, and the fact that SUMC is the sole hospital serving the entire population of the area. This unique situation enables such an epidemiological population-based study as a "captive population" with an almost complete database, as the hospital provides both maternal and pediatric services, free of charge to all the region's residents. This enables the rare opportunity to examine our population for long-term outcomes, with the ability to control for parameters surrounding pregnancy, labor, and delivery.

Nevertheless, some limitations should be addressed when considering the results. First, the actual rates of offspring morbidity are probably underestimated, as most of the GI morbidities listed in the appendix, are cared for in an ambulatory setting, thus not included in the data. Secondly, it appears that although the outcome is statistically significant, the magnitude of the findings is small. In addition, the rates of relocation outside of the region and/or admission at a different facility could not be estimated or accounted for. However, we assume that since this phenomenon probably occurs in similar proportions in all three study groups, it does not affect the study findings. We excluded from the study population children with congenital malformation which were diagnosed during the delivery or immediately following the delivery. Nevertheless, some of the offspring have been diagnosed with anatomical malformation only later on during their childhood, thus not initially excluded. The study focuses on two main comparison groups of amniotic fluid abnormalities during pregnancy, whose causes and implication differ enormously. Nevertheless, combined together, both entities reflect a wider picture of all possible pathological changes in the amount of amniotic fluid, and their long-term effect on the offspring. Moreover, the spectrum is presented in a linear fashion, from low to normal to high amount of fluid. Lastly, the children in the present study were followed only up to the age of 18 years. It is possible that with a longer follow-up, additional morbidities would have surfaced in one or all groups. We conclude that exposure to isolated oligohydramnios in utero appears to increase the risk for pediatric long-term GI morbidity and consequently GI-related hospitalization. Although fetal/neonatal programing may be the underlying explanation for these observations, this remains a speculation at this stage. Further prospective studies are needed to substantiate or refute this hypothesis.

Author contributions AA: manuscript writing. TW: data collection and data analysis. ES: protocol development and manuscript editing. AW: manuscript editing. DL: manuscript editing. GP: manuscript editing

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest. The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval Authors approve, and the study was approved by the local ethical committee, according to the declaration of Helsinki (REB number-SOR-0438-15).

Informed consent This is a retrospective study. The study was approved by the local ethical committee, according to the declaration of Helsinki (REB number-SOR-0438-15).

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