Does Polyhydramnios in Singleton Pregnancies Has Effect on Perinatal Outcome in Absence of Congenital Fetal Anomalies

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Abstract: ***Objective:*** To determine if polyhydramnios in singleton pregnancies has effect on perinatal outcome in absence of congenital fetal anomalies. ***Materials and methods:*** We conducted a retrospective study on pregnant women attending outpatient clinics in Bab Alshaaria university hospital by reviewing their medical files from December 2009 to December 2013 to assess the perinatal outcome in singleton pregnancies with polyhydramnios in absence of congenital fetal anomalies. Finally, 90 cases were included as unexplained polyhydramnios, and 152 cases were included as controls. Preterm delivery (<37 weeks gestational age at birth), low birth weight (<2500 g), very low birth weight (<1500 g), macrosomia (>4000 g), 1- and 5-minAPGAR scores <7, small for gestational age (SGA)[defined as birth weight below the 10th percentile for gestational age], large for gestational age (LGA) [defined as birth weight above the 90th percentile for gestational age] fetuses, C-section rates, incidence of fetal distress, admission to neonatal intensive care unit (NICU) after delivery and neonatal death within the first 7 days were selected as perinatal outcome variables. ***Results:*** Higher incidence of low birth weight (<2500 g), macrosomia (>4000 g), small for gestational age fetuses, large for gestational age fetuses, high C-section rates, fetal distress, admission to neonatal intensive care unit after delivery and neonatal death within the first 7 days in the unexplained polyhydramnios group compared with the control group. Significantly higher incidence preterm labors and low 1- and 5-min APGAR scores were noted in the unexplained polyhydramnios group compared with the control group. ***Conclusion:*** Polyhydramnios is significantly associated with adverse perinatal outcomes, such as low APGAR scores, preterm labour despite exclusion of congenital anomalies from the study population. Detailed antepartum fetal well-being surveillance, intensive intrapartum monitoring and further attention in the postpartum period is warranted in patients with this condition.

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1. Introduction

The amniotic fluid is essential for normal fetal development. It not only provides protection to the fetus from traumatic forces, cord compression, and microbial pathogens, but also plays an integral role in the normal development of the fetal musculoskeletal, pulmonary, and gastrointestinal systems [1]. Changes in amniotic fluid may suggest a pathological process. Pregnancies complicated by oligohydramnios are at higher risk for adverse perinatal outcomes, such as perinatal mortality, preterm delivery, low or very low birth weight; meconium stained amniotic fluid, cesarean delivery, low APGAR scores, and neonatal intensive care admission In contrast, implications for pregnancies complicated by polyhydramnios are not as clear as for oligohydramnios [2].

Polyhydramnios, defined as an excessive amount of amniotic fluid, complicates approximately 0.4-3.3% of all pregnancies [3-5]. Known causes of polyhydramnios include congenital anomalies, fetal aneuploidy, maternal diabetes mellitus, multiple gestation, isoimmunization, and placental abnormalities [6]. The etiology of polyhydramnios is unclear in many cases. In one large series predating the use of antenatal ultrasound, the cause of polyhydramnios was unknown in 34% of cases [6]. The incidence of polyhydramnios has declined over the time due to prevention of Rh-isoimmunization due to the availability of Rh immunoglobulin, and diagnosis and treatment of gestational diabetes. Sonographic detection of structural abnormalities associated with polyhydramnios has led to a decrease in the number of unexplained cases [6-8].

A higher rate of complications during pregnancy has been associated with polyhydramnios assessed either by the single largest pocket measurement or using a semi-quantitative manner [9]. Perinatal morbidity and mortality rates also significantly increase [10, 11].

Amniotic fluid balance is a consequence of complex interactions between fetal and maternal systems. The integration of fluid flow into and out

generally determines the ultimate volume of amniotic fluid. Fetal urination, lung fluid production, swallowing, and membranous absorption contribute to overall fluid balance especially during late gestation. Various disorders and malformations could possibly result with amniotic fluid imbalance, which is generally associated with adverse perinatal outcome. Polyhydramnios is defined as excessive accumulation of amniotic fluid in complicated pregnancies with an incidence ranging from 0.4% to 3.3% [12]. Maternal disorders, such as diabetes, in-utero infections, drug usage, placental abnormalities and fetal conditions as congenital and chromosomal abnormalities, Rh iso-immunization, and multiple gestations, are generally associated with polyhydramnios [12]. Congenital abnormalities such as duodenal, esophageal, or intestinal atresia of fetus are the most common malformations that typically cause gastro-intestinal obstruction and interfere with fetal swallowing and/or absorption resulting with polyhydramnios. However, in about 60% of cases, none of the aforementioned etiologies are causes of polyhydramnios, and it is referred to as idiopathic or unexplained [13]. As unexplained polyhydramnios is a matter of debate in obstetric practice, the aim of this analysis is to investigate especially perinatal outcomes of unexplained polyhydramnios and to evaluate whether it is associated with adverse events.

2. Materials and Methods

We conducted a retrospective study on pregnant women attending outpatient clinics in Bab Alshaaria university hospital by reviewing their medical files from December 2009 to December 2013 to assess the perinatal outcome in singleton pregnancies with polyhydramnios in absence of congenital fetal anomalies which were detected after the 20th week of gestation. Polyhydramnios was defined as amniotic fluid index (AFI) greater than 20 cm using four-quadrant technique according to Phelan *et al.* [14]. For the control group, at least three AFI measurements beginning from the 20th week of gestation and for the polyhydramnios group, weekly AFI measurements beginning from the diagnosis of polyhydramnios until delivery were confirmed within the records.

Inclusion Criteria:

* Single pregnancy.

* No Diabetes mellitus or preeclampsia in the present pregnancy.

*No Congenital anomalies diagnosed in utero or by physical examination at birth. *No placental anomalies.

*No evidence of in-utero infections (toxoplasma, rubella, cytomegalovirus, herpes, syphilis ….).

* Euploidy.

* No Isoimmunization.

*All Patients in our study must be delivered in Bab Alshaaria hospital.

Exclusion Criteria:

* Multiple pregnancies.

* Diabetes mellitus or preeclampsia in the present pregnancy.

*Congenital anomalies diagnosed in utero or by physical examination at birth. *Accompanying placental anomalies.

*Positive evidence of in-utero infections (toxoplasma, rubella, cytomegalovirus, herpes, syphilis ….).

*Aneuploidy.

* Isoimmunization.

*Patients delivered at another institution.

Finally, 90 polyhydramnios cases were selected as the study group. As a control group, 152 consecutive normal singleton pregnancies with unremarkable perinatal history were included in the study if they had at least three AFI measurements ranging between 5 and 20 cm beginning from the 20th week of gestation. Baseline characteristics of both groups are listed in *Table I*. Perinatal outcome variables were as follows: preterm delivery, low birth weight, very low birth weight, macrosomia, 1- and 5-min APGAR scores <7, small for gestational age, large for gestational age fetuses, C-section rates, increase incidence of fetal distress, admission to neonatal intensive care unit after delivery, and neonatal death within the first 7 days. All parameters were compared within the groups *Table II*.

Statistical analysis was performed using Chi-square, Fisher's exact, Mann-Whitney U, and Kruskal-Wallis tests where appropriate, utilizing the Statistical Package for the Social Sciences (SPSS) software. A p value<0.05% was considered statistically significant.

3. Results:

Over about 4 years from December 2009 to December 2013 we retrospectively analyzed perinatal outcome of 242 singleton pregnancies, of that 90 were defined as unexplained polyhydramnios as the first group, and 152 were included as control group.

The mean maternal age was 24.7±4.9 (95% CI: 23.26–26.03) years for study group and 24±4.85 (95% CI: 23.6–24.5) years for controls. Gestational age at onset of polyhydramnios was 31.3±2.7 (22–36) weeks in study population.

The gestational age at the time of delivery ranged from 25–40 weeks, and the mean gestational age in the groups were 38.1±1.7 (95% CI: 37.6–38.6) and 38.9±1.31 (95% CI: 38.4–38.7) weeks, respectively (p<0.05). The mean fetal body weight at time of deliveries in the groups were 3246 ±482 (95% CI: 3126–3368) and 3237 ±442 (95% CI: 3148–3326)

gram, respectively. Perinatal outcome measures of the groups are shown in *Table II*.

Table I Characteristics of the two groups:

Character	Unexplained polyhydramnios (Study Group) [90]	Normal AFI (Control Group) [152]	*p* Value
Maternal age (years)	24.7±4.9	24±4.85	NS
Gestational age at onset of polyhydramnios (weeks)	31.3±2.7	–	–
Gestational age at birth (weeks)	38.1±1.7	38.9±1.31	<**0.05**
Birth weight (g)	3246±482	3237±442	NS
AFI (cm)	24.3±2.2	13±3.65	–

NS: not significant

Table II Perinatal outcome of the two groups:

Character	Unexplained polyhydramnios (Study Group) [90](%)	Normal AFI (Control Group) [152](%)	*p* Value
Preterm delivery(<37 weeks)	15 (16.6)	7(4.6)	*0.011
<1500 g	2 (2.2)	4(2.6)	NS
1500–2500 g	8 (8.9)	5(3.3)	NS
>4000 g	7 (7.8)	7(4.6)	NS
1- APGAR <7	2 7(30)	20(13.1)	*0.007
5 - APGAR <7	6 (6.7)	0	*0.003
SGA fetus	9 (10)	8(5.3)	NS
LGA fetus	3 (3.3)	4(2.6)	NS
C-Section	2 8(31.1)	44(28.9)	NS
Fetal distress	10(11.1)	8(5.3)	NS
Admission to NICU	8 (8.9)	9(5.9)	NS
Neonatal death	3 (3.3)	0	NS

*Significant difference; **NS**: not significant

4. Discussion:

The etiologic factors of polyhydramnios are varied and may include maternal and fetal conditions such as congenital anomalies, diabetes mellitus, isoimmunization, multiple gestations, and placental abnormalities [15,16]. But the cause of polyhydramnios remains idiopathic in most cases (60%), [16] and the precise incidence of associated perinatal outcomes is unclear because the definition of polyhydramnios, subjective impression, and quantitative deepest vertical pocket measurement influence the reported incidence of this entity. Adverse perinatal outcomes in patients with polyhydramnios have been associated with congenital fetal anomalies in numerous studies [17, 18].

Prior studies have identified polyhydramnios as a risk factor for adverse outcomes, higher rates of preterm delivery and increased rates of perinatal morbidity and mortality. These studies were not restricted to cases of unexplained polyhydramnios. [8-10].

Polyhydramnios is one of the common disorders among pregnancies and most often is observed as a result of several maternal and fetal disorders. On the other hand, it is really hard to clear out the cause in majority of the cases. Since exact etiology of unexplained polyhydramnios is still unclear, many studies have been conducted to clarify the actual mechanisms of the regulation of amniotic fluid and even molecular interactions that are involved within regulation. In this perspective, an increasing number of clinical and molecular studies is designed to define the molecular architecture of biologic membranes, which are involved with amniotic fluid regulation. Most recently, increased aquaporin expression has-been reported in the fetal membranes of cases complicated with idiopathic polyhydramnios [19].

Our retrospective study is predominantly highlighting two major perinatal outcomes that may accompany unexplained polyhydramnios cases; as they are high preterm delivery rates and relatively low APGAR scores. A total number of 15 preterm deliveries detected (<37 weeks), (16.6%) in the study group compared with 7 (4.6%) in controls where the difference was statistically significant (p<0.05). Relatively greater number of preterm deliveries alone did not negatively influence mean gestational age and fetal birth weight parameters in the polyhydramnios group, as they were 38.1 weeks and 3246 g, respectively. This might be due to advanced gestational age spectrum of preterm deliveries as the majority of them were detected above the 34th week of gestation. Only two cases were detected under the 28thweek of gestation and the remaining thirteen were

detected between the 34th and 37th week of gestation. Likewise, Pri-Paz etal. Recently reported significantly higher rates of preterm (<37 weeks) and early preterm (<34 weeks) deliveries in their polyhydramnios group compared with controls [20].

Chen et al. also reported higher incidence of preterm deliveries (21 %) in their large retrospective study with mean gestational age of 37.1 weeks and mean fetal birth weight of 2929 g in polyhydramnios group [21]. Furthermore, Dorleijn et al. reported the incidence of preterm delivery as high as 20.5% in their idiopathic polyhydramnios group with the mean gestational age of37.9 weeks and the mean fetal birth weight of 3350 g [22]. As mentioned above, several studies investigating idiopathic polyhydramnios cases underline high preterm delivery rates with relatively normal birth weights and reasonable gestational age; nevertheless, some authors have failed to demonstrate this relation [23]. Potential consequence of uterine over distension due to polyhydramnios was already thought to activate a uterine pressure sensitive system capable of initiating uterine contractility and labor [24]. The same mechanism may be the explanation of the higher rates of premature deliveries in multiple gestations. Additionally, Mazor *et al.* reported that in patients with preterm parturition, polyhydramnios is one of the important variables which contribute to intra- and post-partum mortality [25].

The second remarkable result is the lower 1- and5-min APGAR scores in the study group compared with controls. Relatively higher preterm deliveries may have influenced this result; however, reports are controversial in the literature. Some authors reported low APGAR scores [20-22, 26], whereas others have failed to demonstrate the significant association between idiopathic polyhydramnios and low scores [12, 27]. In the report of Pri-Paz *et al.* significantly low 5-min APGAR scores in the polyhydramnios group that AFI >35 cm were noted compared with controls [20].

In general, APGAR scores reflect fetal status at the time of delivery and may be considered as the indicator of perinatal well-being. Several maternal-perinatal factors including the mode of delivery may influence 1- and 5-min scores. Inadequate fetal oxygen in delivery may also contribute to relatively low scores since Hershkovitz *et al.* demonstrated altered fetal middle cerebral artery (MCA) pulsatility index in idiopathic polyhydramnios group compared with controls [28].

In our study, maternal and perinatal characteristics did not differ significantly, thus low APGAR scores are thought to be the result of relatively higher preterm deliveries. Obviously, study population is too small to be conclusive.

Aneuploidy risk is another questionable issue in idiopathic polyhydramnios cases. Some authors have demonstrated aneuploidy incidence as much as 3.2% [29] and recommended routine screening; however, others revealed that the incidence is around 1% and further invasive approaches are unnecessary unless there are fetal sonographic abnormalities. Dorleijn *et al.* reported only one case of aneuploidy (trisomy 21) in their retrospective analysis of 88 idiopathic polyhydramnios cases [22].

Recently, Pri-Paz *et al.* retrospectively reviewed 527 polyhydramnios cases and finally did not recommend routine amniocentesis in the setting of isolated polyhydramnios without sonographic evidence of other abnormalities [20].

This retrospective study has some limitations; the number of the study group is limited with 90 cases, demographic data are limited with the maternal age, and severity of polyhydramnios was not classified.

In summary, a thorough investigation of the mother and the fetus is mandatory since several maternal disorders and fetal abnormalities should have to be excluded in order to refer a case as idiopathic. For this purpose, careful initial follow-up including fasting glucose and TORCH serology screening is needed. Placenta should have to be evaluated for structural abnormalities.

Aneuploidy screenings and careful second trimester ultrasound investigation is crucial to detect fetal congenital abnormalities. Amniocentesis should be considered for cases with clear evidence of abnormalities and elevated aneuploidy risk. Gestational diabetes screening should be performed in all cases and indirect Coombs test should be considered if there is Rh-immunization.

Clinicians should be aware of chromosomal abnormalities especially for early onset polyhydramnios cases. Monthly AFI assessments starting from the 20th week of gestation and weekly antenatal surveillance beginning from the 32nd week of gestation is recommended. On account of relatively higher preterm delivery rates, antenatal corticosteroids should be taken into consideration. Doppler velocimetry and biophysical profile (BPP) should be considered in severe cases especially near term. Careful examination of the neonates either for syndromical abnormalities or late onset findings is another crucial issue.

Further larger studies are needed to resolve complex mechanisms and to establish universal guidelines

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