Polyhydramnios: Causes, Diagnosis and Therapy

Das Polyhydramnion: Ursachen, Diagnostik und Therapie

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Abstract

Polyhydramnios is defined as a pathological increase of amniotic fluid volume in pregnancy and is associated with increased perinatal morbidity and mortality. Common causes of polyhydramnios include gestational diabetes, fetal anomalies with disturbed fetal swallowing of amniotic fluid, fetal infections and other, rarer causes. The diagnosis is obtained by ultrasound. The prognosis of polyhydramnios depends on its cause and severity. Typical symptoms of polyhydramnios include maternal dyspnea, preterm labor, premature rupture of membranes (PPROM), abnormal fetal presentation, cord prolapse and postpartum hemorrhage. Due to its common etiology with gestational diabetes, polyhydramnios is often associated with fetal macrosomia. To prevent the above complications, there are two methods of prenatal treatment: amnioreduction and pharmacological treatment with non-steroidal anti-inflammatory drugs (NSAIDs). However, prenatal administration of NSAIDs to reduce amniotic fluid volumes has not been approved in Germany. In addition to conventional management, experimental therapies which would alter fetal diuresis are being considered.

Zusammenfassung

Als Polyhydramnion bezeichnet man eine pathologische Vermehrung von Fruchtwasser bei der Schwangeren, die mit einer erhöhten perinatalen Morbidität und Mortalität vergesellschaftet ist. Häufige Ursachen eines Polyhydramnions sind der Gestationsdiabetes, fetale Fehlbildungen, die z. B. zu einem gestörten Schluckvorgang von Fruchtwasser führen, fetale Infektionen und andere seltene Ursachen. Die Diagnostik des Polyhydramnions erfolgt dabei v. a. sonografisch. Die Prognose des Polyhydramnions hängt von der Ursache sowie der klinischen Ausprägung ab: Typische Folgen des Polyhydramnions beinhalten maternale Atembeschwerden, die Frühgeburtlichkeit, den vorzeitigen Blasensprung, regelwidrige Kindslagen, den Nabelschnurvorfall, sowie die postpartale Blutung. Aufgrund einer gemeinsamen Ätiologie mit einem Gestationsdiabetes ist das Polyhydramnion darüber hinaus mit einer fetalen Makrosomie assoziiert. Zur Vermeidung der o. g. Komplikationen bestehen pränatal grundsätzlich 2 Therapieformen: die invasive Entlastungspunktion und die medikamentöse Amnionreduktion mit z. B. Non-Steroidal Anti-inflammatory drugs (NSAID), die jedoch in Deutschland bei dieser Indikation nicht zugelassen sind. Darüber hinaus gibt es in jüngster Zeit experimentelle Therapieansätze, die auf die Beeinflussung der fetalen Diurese zielen.

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Introduction

Polyhydramnios is the term used to describe an excess accumulation of amniotic fluid. This clinical condition is associated with a high risk of poor pregnancy outcomes [1–3]. The reported prevalence of polyhydramnios ranges from 0.2 to 1.6% of all pregnancies [4–7].

Under physiological conditions there is a dynamic equilibrium between the production and resorption of amniotic fluid. Fluid levels are influenced by fetal urination and fetal lung liquid production. Amniotic fluid is reabsorbed by fetal swallowing and intramembranous and intravascular absorption. The relative attribution of each of these mechanisms varies over the course of the pregnancy. A disturbed equilibrium can be the result

of compromised swallowing function or increased urination and can lead to polyhydramnios [8–11].
A fetus close to term will produce between 500–1200 ml urine and swallow between 210–760 ml of amniotic fluid per day. Even small changes in this equilibrium can result in significant changes in amniotic fluid volumes [9–11].

Etiology

An underlying disease is only found in 17% of cases in mild polyhydramnios. In contrast, an underlying disease is detected in 91% of cases in moderate to severe polyhydramnios [5]. The literature lists the following potential etiologies [5,7,12–19]:

- fetal malformations and genetic anomalies (8–45%)
- maternal diabetes mellitus (5–26%)
- multiple pregnancies (8–10%)
- fetal anemia (1–11%)
- other causes, e.g. viral infections, Bartter syndrome, neuromuscular disorders, maternal hypercalcemia. Viral infections which can lead to polyhydramnios include parvovirus B19, rubella, and cytomegalovirus. Other infections, e.g. toxoplasmosis and syphilis, can also cause polyhydramnios [80–82].

Advances in detailed ultrasound scanning and the prevention of Rhesus isoimmunization in the last decades have changed the relative frequency of these etiologies and significantly reduced the number of idiopathic cases [12–19].
Well-known malformations which impair the swallowing reflex include esophageal atresia, duodenal atresia [16,17] and neuromuscular disorders such as myotonic dystrophy. Increased urine production, as occurs with increased cardiac output associated with fetal anemia, can also result in increased production of amniotic fluid [20,21]. These changes can also occur in the context of chromosomal disorders such as trisomy 21 and different syndromes. Duodenal atresia is the most important etiology in cases with trisomy 21 [79].
Poorly managed gestational diabetes is associated with fetal macrosomia and polyhydramnios but the pathogenesis has not been elucidated yet [22]. One possible explanation is fetal hyperglycemia resulting in increased osmotic diuresis which subsequently leads to polyuria. This theory is supported by evidence of a strong association with high glycosylated hemoglobin values (HBA_{1c}) in cases with polyhydramnios [22,23]. According to the AWMF S3-guideline, polyhydramnios can be an indication of diabetogenic fetopathy. However, due to the wide range in amniotic fluid volumes, polyhydramnios does not play an important role in monitoring gestational diabetes [68]. The prevalence of polyhydramnios in maternal cases with diabetes mellitus is 18.8% [23]. As the cause could also be fetal metabolic syndrome, children born after pregnancy complicated by polyhydramnios should be followed up by a pediatrician [24,25].

Ultrasound Assessment of Amniotic Fluid Volume

Ultrasound and subjective or semi-quantitative assessment is used to evaluate amniotic fluid volumes. With the subjective method, the examiner estimates the volume of amniotic fluid based on personal impressions of the amniotic fluid depot. The sonographer's experience plays an important role here [26]. When evaluating cases of oligo- or polyhydramnios, the use of biometric measurements and references is more accurate when examiners are less experienced, while evaluation based solely on subjective assessment is associated with good results if done by an experienced examiner [27].
Various semi-quantitative methods to measure amniotic fluid volumes have been described. But these methods also have their limitations which must be taken into account [28].

Single deepest pocket measurement

For this type of measurement the uterus is divided into four quadrants. The amniotic fluid volume is measured vertically in the deepest amniotic fluid pocket. Values below 2 cm indicate oligohydramnios, values over 8 cm indicate polyhydramnios [30]. The advantage of this method is its simplicity, making it the most commonly used method in practice. It is also the method of choice in multiple gestation. In cases with multiple gestation, a range of 3–8 cm is defined as normal. With this method, polyhydramnios is classified as mild, moderate or severe. Mild polyhydramnios is characterized by a value of 8–11 cm, moderate polyhydramnios by a value between 12–15 cm and severe polyhydramnios by values above 16 cm [86].

The 4-quadrant method (AFI – Amniotic Fluid Index)

With this method, the deepest amniotic pocket in each of the four quadrants is measured vertically and the values added together. The uterus is divided vertically into two halves by an imaginary line along the linea nigra. An imaginary horizontal line through the umbilicus divides the uterus into an upper and a lower half. During measurement the transducer is held at right angles to the sagittal plane of the patient's abdomen. The transducer should not be tilted along the maternal abdomen, i.e. it must be kept at a right angle. The measured amniotic fluid pockets must be free of fetal extremities and the umbilical cord and must be at least 0.5 cm wide. The Amniotic Fluid Index (AFI) is the sum of measurements of all four quadrants. According to one study group, AFI values between 8.1 and 18 cm are normal, values between 5.1 und 8.0 cm indicate oligohydramnios, an AFI value of less than 5.0 cm indicates severe oligohydramnios and a value above 18 cm is classified as polyhydramnios [31].
Based on AFI values obtained during prenatal screening, some clinicians categorize polyhydramnios into three groups according to severity: mild polyhydramnios (AFI of 25–30 cm), moderate polyhydramnios (30.1–35 cm) and severe polyhydramnios (≥ 35.1 cm) [87].
Moore und Cayle [32] investigated the distribution of AFI measurements in a population with normal pregnancies. In contrast to the definition of oligohydramnios proposed by Phelan et al. (AFI less than 5 cm [31]) they found that an AFI of 5 cm was only found in 1% of normal pregnancies. Intraobserver variation ranged between 0.5 and 1 cm, and interobserver variation was between 1 and 2 cm. Taking the calculated average of three measurements is recommended to achieve the greatest accuracy, particularly when the AFI is less than 10 cm [32]. The use of color flow Doppler has the advantage that umbilical cord loops are detected more easily. But, according to a retrospective study by Zlatnik et al. [34], AFI measured with color flow Doppler overestimated oligohydramnios and underestimated polyhydramnios if standard AFI tables (obtained without color flow Doppler) were used [33,34].
It should be noted that the pressure exerted by the transducer can change AFI and single deepest pocket measurements. If the pressure is minimal, AFI increases by 13%, while if strong pressure is exerted, AFI is underestimated by 21% [35–38].

Amniotic fluid quantification in the German Maternity Guidelines

In the German Maternity Guidelines, assessment of amniotic fluid is a standard examination in prenatal care. Oligohydramnios and polyhydramnios are considered indicative of a developmental disorder. If there is a suspicion of a developmental disorder, regular follow-up examinations and further diagnostic tests are recommended [69]. The diagnosis of polyhydramnios appears to be independent of gestational week. An enlarged amnion at the first ultrasound scan in the 7th week of gestation is associated with early embryonic death [70,71]. However different constellations can affect prognosis. Polyhydramnios combined with a small for gestational age (SGA) fetus has a particularly poor prognosis as this combination is associated with a high incidence of malformations. Typically, trisomy 18 is a suspected diagnosis [72,73]. In a monochoriotic diamniotic twin pregnancy with polyhydramnios in the amniotic sac of one fetus and oligohydramnios in the amniotic sac of the other, the cause is often feto-fetal transfusion syndrome [74–77].

Comparison of the two methods (AFI and SDP)

The goal of amniotic fluid volume quantification is to detect amniotic fluid pathologies associated with poor outcomes rather than to determine the actual amniotic fluid volume [29]. A systematic review of randomized studies found no evidence that one method was superior to another [39,40,41,89]. Significantly more cases of oligohydramnios were diagnosed using the AFI method. But there were no significant differences between methods with regard to prognosis of perinatal outcome in post-term pregnancies. However, single deepest pocket (SDP) measurement is the method of choice in multiple pregnancies as it is simpler to perform and equally effective [90–98].

Further Diagnostic Tests when Polyhydramnios is Present

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Ultrasound investigation

The fetus should be examined carefully during fetal organ screening. The anomalies most commonly missed at screening are tracheoesophageal fistula, cardiac septal defects and cleft palate [7]. If a fetal malformation or several soft markers are present, fetal karyotyping is recommended after obtaining informed parental consent in accordance with the German Genetic Diagnosis Act [42–45]. In a large study, the prevalence of aneuploidy in fetal anomalies was found to be 10% (95% CI: 5–19%) [7]. The risk of fetal malformation in cases with severe polyhydramnios has been reported to increase to 11%, but this figure is still discussed controversially. The risk of fetal anomalies is 1% with mild polyhydramnios and 2% with moderate polyhydramnios 2% [99]. In Germany, a detailed ultrasound scan done in an experienced prenatal center (DEGUM II/III [German Society for Ultrasound Medicine]) is recommended if there is a high degree of suspicion of fetal malformation.

Some causes, e.g. swallowing disorders and tracheoesophogeal fistula or atresia can be completely overlooked by ultrasound. In this case, fetal MRI can offer a better alternative in the diagnosis of tracheoesophogeal fistula or atresia in utero [82–85].

Laboratory tests

Laboratory tests to identify causes of polyhydramnios should include:

- 75 g oral glucose tolerance test (OGTT) to exclude gestational diabetes
- maternal diagnostic testing for infection (ToRCH serology)
- if there is a suspicion of fetal anemia or fetal hydrops, tests to exclude immunological causes (maternal blood group, Rhesus factor, screening for antibodies) and hematological disorders (possibly Kleihauer-Betke test to exclude fetomaternal hemorrhage) are indicated. The literature also lists certain drugs, e.g. lithium, which are associated with a higher incidence of polyhydramnios. Lithium is a psychotropic drug prescribed prenatally, e.g. to treat bipolar disorders [100].

Severe fetal anemia is frequently associated with pleural and pericardial effusion, ascites and/or skin edema. Measurement of middle cerebral artery peak systolic velocity is a useful method to diagnose fetal anemia; fetuses with a peak systolic velocity > 1.5 MoM have a strong risk of anemia.

Intrauterine infection may be suspected based on maternal symptoms or fetal abnormalities such as hydrocephalus due to toxoplasmosis.

Prognosis

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The risk of the following obstetric complications is increased when polyhydramnios is present due to over-expansion of the uterus [1,46,47]:

- maternal dyspnea
- preterm labor
- premature rupture of membranes
- abnormal fetal presentation
- umbilical cord prolapse
- postpartum hemorrhage
- fetal macrosomia due to maternal diabetes mellitus
- hypertensive disorders of pregnancy
- urinary tract infections

These risks vary depending on the severity and etiology of the polyhydramnios [1–3]. Perinatal mortality increased 13-fold when the single deepest pocket was less than 2 cm; when the SDP was less than 1 cm, perinatal mortality increased 47-fold [26].

A prospective longitudinal study of normal singleton pregnancies lists the following potential complications [34]:

- higher rates of cesarean sections for fetal indications
- higher rates of admission to neonatal intensive care units
- higher birth weight
- lower 5-minute Apgar scores

In a large study of 85 000 pregnancies, of which 3900 pregnancies had an increased AFI, it was found that polyhydramnios was an independent risk factor for perinatal mortality [48]. Small for gestational age (SGA) fetuses with polyhydramnios had the poorest prognosis [78].

Treatment Options to Reduce Amniotic Fluid Volume

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Treatment consists of reducing the volume of amniotic fluid to improve maternal well-being and prolong the pregnancy. The following methods are used to reduce amniotic fluid volumes:

- amnioreduction (therapeutic amniocentesis) [53–55]
- pharmacological treatment [49–52]

Amnioreduction

To date, this method has not been evaluated in randomized or controlled studies, but it offers a clear clinical benefit if done after careful diagnostic evaluation. However, there is no consensus regarding the volume of aspirated amniotic fluid, the speed of aspiration and the use of tocolytics or antibiotics. The intervention is usually concluded when ultrasound examination shows an AFI of 15 to 20 cm or if intra-amniotic pressure drops to < 20 mmHg [53,66]. In some cases, the intervention had to be terminated due to maternal discomfort or premature placental abruption. Tocolytics are routinely used as prophylaxis to prevent onset of preterm labor.

Complications occur in 1–3 % of cases and can include premature labor, placental abruption, premature rupture of membranes, hyperproteinemia and amniotic infection syndrome [52,54]. After the procedure, regular monitoring of amniotic fluid volumes is recommended, with monitoring done every 1 to 3 weeks.

Prostaglandin synthetase inhibitor

Prostaglandin synthetase inhibitors stimulate fetal secretion of arginine vasopressin, resulting in vasopressin-induced antidiuresis [49,57,58,62]. Reduced renal blood flow reduces fetal urine production. These substances can also inhibit fetal lung liquid production or increase reabsorption rates [56].

However, prostaglandin synthetase inhibitors have not been approved for this indication in pregnancy in Germany.

While these substances are used as an analgesic or in anti-inflammatory therapy in the 1st and 2nd trimesters of pregnancy, patients are advised against using these substances after the 28th week of gestation [88]. It should be noted that the use of these drugs is not generally approved in pregnancy.

Sulindac

Sulindac is a non-steroidal anti-inflammatory drug; use of sulindac can also lead to a reduction of amniotic fluid volume. There are some reports that sulindac decreases pulsatility in fetal ductus arteriosus less than indomethacin [58–61]. However, the efficacy of sulindac has not been confirmed by further studies yet.

Potential Future Experimental Therapies

As fetal urine production constitutes the main source of amniotic fluid and changes in urine production can significantly change the dynamics of amniotic fluid volumes, the effect of intra-amniotic administration of arginine vasopressin was investigated. Arginine vasopressin is absorbed into fetal plasma from the intra-amniotic fluid. The effects of a V2 receptor agonist, deamino(D-Arg8)-vasopressin, on fetal plasma arginine vasopressin immunoreactivity, fetal urine production and swallowing was investigated in 6 individual ovine pregnancies. It was demonstrated that intra-amniotic administration of deamino(D-Arg8)-vasopressin resulted in persistent fetal antidiuresis with no cardiovascular effects and no changes in fetal swallowing. Even though the data do not permit a general conclusion to be drawn, these results indicate this could be a potential therapy for polyhydramnios [63].

Another potential therapy is based on mRNA expression in chorion and amnion cells of aquaporin (AQP) 1, 8 und 9 in amniotic fluid, which is increased in polyhydramnios. Aquaporins are water channel proteins which regulate the flow of water across cellular membranes. AQP1 expression could represent a compensatory response to polyhydramnios. The effect of reducing this protein on polyhydramnios requires further study [64,65]. The efficacy and safety of these experimental therapeutic approaches should be investigated in prospective randomized studies.

Monitoring of Pregnancies with Polyhydramnios

In view of the increased perinatal mortality and morbidity associated with pregnancies with polyhydramnios, careful monitoring is recommended [46].

Expectant management vs. intervention

There are no prospective randomized studies comparing expectant management to active intervention in idiopathic polyhydramnios [1]. Intervention is generally recommended in cases with severe maternal discomfort or obstetric complications, e.g. premature labor.

Delivery

Fetal head presentation should be checked several times during labor, as fetal position change to breech presentation or transverse lie can occur intrapartum.

Spontaneous rupture of membranes can lead to acute uterine decompression with the risk of cord prolapse or placental abruption. Artificial rupture of membranes should therefore only be done under controlled conditions.

Although polyhydramnios does not constitute a contraindication for the application of oxytocin or prostaglandins, these substances should be administered with care. There is an increased risk of atonic bleeding and amniotic-fluid embolism postpartum [57,67].

Conclusion

Polyhydramnios diagnosed on ultrasound requires further maternal and fetal diagnostic tests. Maternal gestational diabetes should be excluded and maternal ToRCH screening is recommended. Detailed morphological testing should be planned for the fetus. Delivery in a perinatal center is recommended.

Conflict of Interest

None.

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