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Amniotic Fluid Dynamics

William M. Gilbert, MD*

Author Disclosure
Dr. Gilbert did not disclose any financial relationships relevant to this article.

Objectives
After completing this article, readers should be able to:

1. Describe clinical assessments of amniotic fluid volume.
2. Explain the processes of amniotic fluid formation and removal.
3. Describe the presentations and treatments for oligohydramnios and polyhydramnios.

Introduction
Fortunately for most healthy pregnant women, amniotic fluid (AF) is an unimportant byproduct of the delivery. Little attention, if any, is paid to the AF unless meconium staining occurs in labor. It is only in the presence of certain complications that may compromise fetal well-being that any interest is taken in the AF. When there is too much AF (polyhydramnios) or too little (oligohydramnios), perinatal morbidity or mortality may be increased significantly, raising sudden concern among patients and clinicians. When severe oligohydramnios occurs in the second trimester, the perinatal mortality rate approaches 90% to 100%. (1)(2)(3) Similarly, with severe polyhydramnios in mid-pregnancy, the perinatal mortality rate can be greater than 50%. (4)(5) Attempts to study abnormalities of AF are hindered by the realization that little is known about the processes involved in the regulation of normal amniotic fluid volume (AFV).

This review examines the limited information available on the normal physiology of AFV regulation, including routes of formation, removal, and regulation and the changes in AF composition across gestation. Additionally, the clinical impact and treatment options on disease conditions are discussed.

Normal Amniotic Fluid Volume
Attempts to measure actual AFV are limited by the invasiveness required to access the amniotic cavity. The most common method is injection of an inert dye into the amniotic cavity via amniocentesis, followed by timed removals of AF to determine a dilution curve. (6)(7)(8)(9) This method has been shown to be accurate compared with actual measurement of AF, but because of its invasive nature, has limited application to clinical practice. Brace and Wolf (10) examined the literature to the time of their publication (1989) and identified all published measurements of actual AFV in 12 studies that included 705 individual AFV measurements (Fig. 1). They documented a wide variation in AFV for each week of gestation, which became more pronounced as gestational age advanced. The largest variation in AFV occurred at 32 to 33 weeks of gestation, with 5th and 95th percentiles being 400 and 2,100 mL, respectively. Although this represents a large “normal range,” the most interesting factor was that average AFV remained constant from 22 weeks to 39 weeks of gestation. The average AFV was the same for a fetus weighing approximately 500 g up to a term fetal weight of 3.5 kg, suggesting some form of regulation.

Clinical Assessments of Amniotic Fluid Volume
Initial attempts to determine AFV clinically included direct uterine palpation. If the uterus was large for gestational age or if the fetus could not be palpated by Leopold maneuvers, polyhydramnios was diagnosed. The ultimate diagnosis of polyhydramnios was made at the time of delivery. Oligohydramnios often was considered a diagnosis if the uterus measured small for gestational age or if the fetus could be palpated easily. Methods of determining AFV by palpation are limited by their subjective nature and poor interobserver reliability.

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With the advent of real-time ultrasonography, AF could be seen, and attempts to measure it began. Initial ultrasonographic estimations of AFV were made by measuring the largest vertical pocket (LVP) of AF (11) or the largest two-dimensional pocket of AF. (12) Chamberlain and associates (12) and others (13) demonstrated that when the LVP was less than 1 cm, perinatal morbidity was increased, and when it was less than 0.5 cm, the perinatal mortality rate was increased. The use of small cutoff values for the LVP identified high-risk groups but missed other patients who had higher values of the LVP but significant perinatal morbidity.

Attempts to improve the sensitivity for measuring AFV by ultrasonography resulted in the amniotic fluid index (AFI), which is the measurement of the LVP in each of four quadrants of the pregnant uterus. Initially termed the AFI by Phelan and associates (14) and more extensively studied by others, (15) the normal range of the AFI can be seen in Figure 2. This graph of the AFI looks fairly similar to the nomogram of AFV as a function of gestational age (Fig. 1), including wide ranges at each gestational age and a consistent average AFI from 22 weeks of gestation until term. The AFI normal range varies for each gestational age, suggesting that a single value for the AFI does not determine the upper (or lower) limits of normality. The clinician must know the gestational age to determine the individual 5th and 95th percentiles. Today, the AFI is used widely to estimate the

AFV in pregnancy, despite poor sensitivity documented in studies comparing AFI with measured AFV by dye dilution techniques. (6)(7)(8)(9)(16)

Amniotic Fluid Formation
Fetal Urine
The largest single source of AF is fetal urine. The human fetus begins to excrete urine by the end of the first trimester and continues to excrete it in ever-increasing volumes until term. The primary animal model used to study fetal urine production is the fetal sheep. (17)(18)(19) The fetal sheep is similar in size to the human and excretes approximately 200 to 1,200 mL/d of urine in the last third of pregnancy. (17)(20)(21) Human fetal urine production has been measured by ultrasonography. Wladimiroff and Campbell (22) initially determined a fetal urine production rate of 230 mL/d at 20 weeks of gestation that increased to 655 mL/d at term by measuring the change in bladder volume every 15 minutes. Others reported similar urine production rates using the same technique. (23)(24)(25)(26) When Rabinowitz and colleagues (27) increased the frequency of bladder volume measurement to every 2 to 5 minutes, they found a much greater produc-
tion rate of 1,224 mL/d. Figure 3 demonstrates the human fetal urine production rate of the major studies using change in bladder volume by ultrasonography. (22)(23)(24)(25)(26)(27)

Lung Liquid
Fetal lung liquid also plays a role in AF formation. For years, most investigators believed that there was a net movement of AF into the fetal lungs (respiration of AF), as demonstrated by the finding of meconium (aspiration) within the lungs of certain newborns. (28) Fetal sheep studies, however, document a net outflow of fetal lung liquid (400 mL/d), 50% of which is swallowed and 50% of which exits by the mouth, entering the amniotic cavity. (29)(30)(31) In humans, indirect evidence confirms that lung liquid enters the amniotic cavity, based on the finding of surfactant within the AF at term.

Amniotic Fluid Removal

Fetal Swallowing
Fetal swallowing is the primary route by which AF exits the amniotic cavity. This route of AF removal has been studied in multiple animal models, primarily the sheep fetus. Swallowing appears to increase with advancing gestational age. Sherman and associates (32) reported that the ovine fetus swallows in bouts lasting 2 minutes and at volumes of 100 to 300 mL/kg per day. This rate equals 350 to 1,000 mL/d for a 3.5-kg fetus at term.

Swallowing in the human fetus was studied in the 1960s by the injection of compounds into the amniotic compartment prior to delivery by cesarean section. Pritchard (28)(33) studied both healthy fetuses and those that had anencephaly by injecting radioactive chromium-labeled erythrocytes and diatrizoate sodium/meglumine into the amniotic compartment and found swallowing rates of 72 to 262 mL/kg per day. Using a similar technique, Abramovich (34) found that fetal swallowing increased with advancing gestational age, with swallowing rates similar to those cited by Pritchard. Measured swallowing volumes cannot account for the removal of the large volume of fetal urine and lung liquid that enters the amniotic cavity every day. Other routes of AF clearance must be present to explain the differences.

Intramembranous Absorption
The route of AF removal that explains the differences between fetal urine and lung liquid production and swallowing is termed intramembranous absorption. (35)(36)(37)(38). This route of absorption involves direct absorption of AF from the amniotic cavity into blood within fetal vessels on the fetal surface of the placenta. The significant osmotic gradient (Fig. 4) between AF and fetal blood results in a major driving force for the movement of water and solutes out of the amniotic cavity. Intramembranous absorption has been studied in
the fetal sheep and rhesus monkey. Reports in humans suggest that intramembranous absorption plays a major role in AFV regulation. The animal studies suggest that a minimum of 200 to 500 mL/d leaves the amniotic compartment under normal physiologic conditions. Intramembranous absorption can be increased tenfold under experimental conditions in the sheep fetus, further suggesting a regulatory function. All of the measured and potential routes of AF entry and removal roughly add up to a balanced equation (Fig. 5).

Oligohydramnios

Oligohydramnios is one of the common indications for antepartum testing at term and in the postdate period. Its incidence varies, depending on the particular definition used, but is reported to be approximately 1% to 3%. The animal studies suggest that a minimum of 200 to 500 mL/d leaves the amniotic compartment under normal physiologic conditions. Intramembranous absorption can be increased tenfold under experimental conditions in the sheep fetus, further suggesting a regulatory function. All of the measured and potential routes of AF entry and removal roughly add up to a balanced equation (Fig. 5).

Preterm Oligohydramnios

When severe oligohydramnios occurs prior to term gestation, the perinatal mortality rate can approach 100%. The indication for decreased or absent AF (e.g., renal agenesis, marked IUGR) usually predicts survival. Table 1 lists many of the causes of oligohydramnios from either the maternal or fetal condition. The definition of oligohydramnios from studies in which the true volume was measured ranged from 200 to 500 mL at term gestation. Using ultrasonography to determine the LVP, Chamberlain and associates found a 50-fold increase in the perinatal mortality rate with a value of less than 1 cm. It was this early study that alerted clinicians to the possible significant high risk of oligohydramnios at this level of LVP. The major drawback of the study was the codiagnosis (40%) of intrauterine growth restriction (IUGR) and other high-risk factors such as hypertensive disorders in the mother. It has become clear that oligohydramnios in concert with other high-risk conditions is associated with increased perinatal morbidity and mortality. When oligohydramnios is diagnosed in the postdate period, there is an increased risk of meconium staining of the AF, meconium aspiration syndrome, fetal distress in labor, and increased cesarean section rates. With severe oligohydramnios in cases of IUGR or maternal hypertensive disorders, delivery often is indicated to decrease the perinatal mortality rate.

Much more common is the mother who presents with the isolated finding of oligohydramnios. Often, results of the cervical examination are not favorable for labor induction, but because of the oligohydramnios and fear of a poor outcome, the patient undergoes a trial of induction that frequently ends in cesarean section. Recent studies have shown that in otherwise low-risk women, the finding of isolated oligohydramnios is not an indication for induction. Magann and associates examined 1,001 high-risk women undergoing antepartum testing and found those who had AFIs of less than 5 cm (19%) had equal perinatal outcomes to those who had normal AFIs. Others found similar outcomes when high-risk women were examined and separated into normal and low AFV. It is important to remember that in cases of isolated oligohydramnios with a normally grown fetus, the absence of other high-risk maternal conditions, and an unfavorable cervix, the patient may be a candidate for observation or possible therapeutic intervention to increase the AFV.

Treatment

The status of maternal and fetal fluids is tightly linked, with dehydration in one resulting in dehydration in the...
other. Goodlin and associates (48) reported that low maternal intravascular volume was associated with an increase in idiopathic oligohydramnios. The oligohydramnios improved with maternal hydration and correction of low intravascular volume. (48) Kilpatrick and colleagues (49)(50) examined the effects of maternal oral hydration on the AFI among women who had oligohydramnios and those who had normal AFIs. They studied women who presented to their fetal testing center with a low AFI and randomized them to drinking 2 L of water or the usual amount of liquids followed by repeat AFI measurement at least 2 to 4 hours later. A significant increase in AFI (24%) was seen in the oral hydration group compared with the unhydrated group. (49) In the second study in a clinical research center, women who had normal AFIs similarly were randomized to drinking 2 L of water. An increase of 3 cm in the AFI was reported with oral hydration over 4 to 6 hours. (50) Other researchers have found that oral or intravenous hydration improves the AFI, and oral hydration generally can be used when isolated oligohydramnios has occurred before the postdate period. For the normal pregnant woman who carries a normally grown fetus before 40 to 41 weeks of gestation, isolated oligohydramnios may be treated with oral hydration and follow-up in 4 to 7 days.

The use of amnioinfusion in labor has been reported to be successful in cases of variable heart rate decelerations and thick meconium. (51)(52)(53)(54)(55)(56) A recent large, prospective, multicenter, randomized trial compared amnioinfusion with controls among all mothers who had thick meconium. (57) No improvement in neonatal outcome or change in cesarean section rate was seen with amnioinfusions in labor.

**Polyhydramnios**

Previously, polyhydramnios was diagnosed when the uterus was large for gestational age or the fetus could not be easily palpated by Leopold maneuvers. The diagnosis was either confirmed or refuted by the AFV at the time of delivery. Like oligohydramnios, polyhydramnios can result in a marked increase in perinatal morbidity and mortality, depending on the AFV, the presence of other fetal or placental abnormalities, and when in gestation it occurs. (4) Severe polyhydramnios in mid-gestation usually is associated with congenital malformations, (with or without aneuploidy) and monozygotic twins. (58) The maternal and fetal causes of polyhydramnios are displayed in Table 2.

Ultrasonography has been used to measure or estimate AFV. Initial attempts employing the LVP reported a value of greater than 8 cm as representing polyhydramnios. (58) These investigators categorized patients who had polyhydramnios into three groups, depending on the LVP measurement: mild (LVP 8 to 11 cm) (79% of cases), moderate (LVP 12 to 15 cm) (16.5% cases), and severe (LVP 16+ cm) (5% of cases). The perinatal mortality rate was 127.5 per 1,000 for all cases of polyhydramnios, which corrected to 58.8 per 1,000 when lethal malformations were removed. (58) This perinatal mortality rate was greatly increased over background rates. Causes of polyhydramnios could be determined in only 16% of the milder forms compared with almost 90% of moderate or severe cases.

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**Table 1. Fetal and Maternal Causes of Oligohydramnios**

<table>
<thead>
<tr>
<th>Fetal Conditions</th>
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<tbody>
<tr>
<td>• Spontaneous rupture of the membranes</td>
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<tr>
<td>• Premature rupture of the membranes</td>
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<tr>
<td>• Abnormal placenta—elevated MSAFP/MSHCG</td>
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<tr>
<td>• Renal agenesis or obstructed uropathy</td>
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<td>• Postmaturity syndrome</td>
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<table>
<thead>
<tr>
<th>Maternal Conditions</th>
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<tbody>
<tr>
<td>• Antiphospholipid syndrome</td>
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<tr>
<td>• Dehydration—hypovolemia</td>
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<tr>
<td>• Hypertensive disorders</td>
</tr>
<tr>
<td>• Uteroplacental insufficiency</td>
</tr>
<tr>
<td>• Idiopathic</td>
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MSAFP = maternal serum alpha-fetoprotein, MSHCG = maternal serum human chorionic gonadotropin

**Table 2. Maternal and Fetal Causes of Polyhydramnios**

<table>
<thead>
<tr>
<th>Maternal Conditions</th>
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<tbody>
<tr>
<td>• Idiopathic</td>
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<td>• Poorly controlled diabetes</td>
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<table>
<thead>
<tr>
<th>Fetal Conditions</th>
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<tbody>
<tr>
<td>• Congenital anomalies</td>
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<tr>
<td>—Central nervous system abnormalities</td>
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<tr>
<td>—Cystic hygromas</td>
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<td>—Gastrointestinal obstruction</td>
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<td>—Nonimmune hydrops</td>
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<tr>
<td>—Sacrococcygeal teratoma</td>
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<tr>
<td>—Aneuploidy</td>
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<tr>
<td>• Twin transfusion syndrome</td>
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<td>• Muscular dystrophy syndromes</td>
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</table>
With the increased clinical use of the AFI compared with the LVP, investigators began to study the AFI. Moore and Cayle (15) reported the AFI across gestation, concluding that the AFI must be referenced to gestational age. The upper limit of normal for the AFI at any point in gestation occurred at 35 weeks of gestation and was 27.9 cm (Fig. 2). This value clearly would be abnormal earlier or later in gestation.

Third Trimester Polyhydramnios
When polyhydramnios occurs in the last third of pregnancy, it is usually mild and not associated with a structural defect. (58) Patients who have persistent polyhydramnios and do not have any structural defects still have an increase in perinatal mortality rate and should be watched closely. (59) One of the most common causes of polyhydramnios in the third trimester is poorly controlled or undiagnosed diabetes. All women should be screened for gestational diabetes at some point in their pregnancies, usually by 28 weeks’ gestation. If their initial test result is normal, and idiopathic polyhydramnios develops near the end of pregnancy, retesting for gestational diabetes may be appropriate.

Treatment
The underlying cause of the polyhydramnios usually directs the treatment. Milder forms of the disease that do not involve congenital malformations require either follow-up repeat measurement of the AFI or antepartum testing if the mild polyhydramnios persists.

For pregnancies complicated by the twin-twin transfusion syndrome, the two treatment modalities of amnioreduction and laser ablation of the vascular connections on the surface of the placenta have been shown to improve pregnancy outcome. Laser ablation currently is performed in mid-pregnancy and, if effective, “cures” the placental cause of the polyhydramnios. (5)(60) Ongoing multicenter trials are comparing amnioreduction with laser ablation for the treatment of twin-twin transfusion syndrome.

EDITOR’S NOTE. For further information about polyhydramnios, in either singleton or twin pregnancies, see the articles by Dr John Yeast in this issue of NeoReviews.

References
19. Mellor DJ, Slater JS. Daily changes in foetal urine and relationships with amniotic and allantoic fluid and maternal plasma during the last two months of pregnancy in conscious, unstressed ewes with chronically implanted catheters. J Physiol. 1972;227:503–525
### NeoReviews Quiz

1. Amniotic fluid volume varies substantially at each week of human gestation, as reflected in the wide range of normal values. Of the following, the largest variation in amniotic fluid volume occurs at the gestational age of:

   A. 26 to 27 weeks.
   B. 29 to 30 weeks.
   C. 32 to 33 weeks.
   D. 35 to 36 weeks.
   E. 38 to 39 weeks.

2. Deviations in amniotic fluid volume, as seen with polyhydramnios or oligohydramnios, are associated with significant perinatal morbidity and/or mortality. Sequential assessment of amniotic fluid volume, therefore, is an important part of clinical care during pregnancy. Of the following, the most widely used and accurate method for estimating amniotic fluid volume is by:

   A. Determination of dye dilution by timed amniocentesis.
   B. Palpation of the fetus by the Leopold maneuver.
   C. Palpation of the uterus for fundal height.
   D. Ultrasonographic measurement of the amniotic fluid index.
   E. Ultrasonographic measurement of the largest vertical pocket.

3. Amniotic fluid volume is determined by a balance between the rate of its production and the rate of its removal from the amniotic cavity. Experimental studies in sheep and observations in humans have shown that the amniotic fluid volume is tightly regulated. Of the following, the function that plays a major role in regulation of the amniotic fluid volume is:

   A. Fetal lung fluid secretion.
   B. Fetal swallowing.
   C. Fetal urine formation.
   D. Intramembranous absorption.
   E. Transmembranous flux.
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