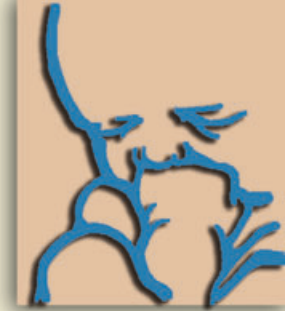


Amniotic Fluid Disorders

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CHAPTER 31

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KEY ABBREVIATIONS

Amniotic fluid	AF
Amniotic fluid index	AFI
Amniotic fluid volume	AFV
Largest vertical pocket	LVP
Intrauterine fetal death	IUFD
Intrauterine growth restriction	IUGR
Neonatal intensive care unit	NICU
Perinatal mortality rate	PMR
Premature rupture of the membranes	PROM
Twin-to-twin transfusion syndrome	TTS

INTRODUCTION

For most pregnant women and their health care providers, amniotic fluid (AF) is an unimportant byproduct of the delivery. With a normal pregnancy, little attention is paid to the AF unless meconium staining occurs in labor. It is only when certain complications of pregnancy present, compromising fetal well-being, that any interest is taken in the AF. The conditions of polyhydramnios (too much AF) or oligohydramnios (too little AF) create the greatest concern to patients and health care providers. As an example, with significant oligohydramnios in the second trimester, the perinatal mortality rate (PMR) approaches 90 to 100 percent.¹⁻³ Likewise, with marked polyhydramnios in midpregnancy, PMR can be higher than 50 percent.^{4,5} Although these two extreme conditions are rare, other less drastic examples are much more common. Efforts to study abnormalities of AF are complicated by the fact that little is known about the processes involved in normal amniotic fluid volume (AFV) regulation. Rarely in modern medical research are the processes

that underlie normal physiology so poorly understood. In studying a particular disease state, knowledge of normal physiology usually assists the researcher in determining the pathophysiology of a particular disease. However, many of the disease states associated with the extremes of AFV are better understood than is the normal physiology of AF.

In this chapter, we explore what is known about the normal mechanisms effecting the formation and removal of AF, including fetal urination, swallowing, lung liquid, and intramembranous absorption.⁶⁻⁸ In addition, we examine the changes in AFV and composition across gestation, in order to help us understand its normal regulation. We then review the abnormalities of AFV, including oligohydramnios and polyhydramnios, and the possible underlying causes. Finally, we examine the various treatment options available for AFV abnormalities. The goal of the chapter is to offer the reader a complete understanding of the known mechanisms and functioning of AFV regulation, and their connection with disease states.

NORMAL AMNIOTIC FLUID VOLUME

As a result of various limitations, attempts to measure actual AFV are difficult. It is not easy to get near, or into, the amniotic compartment. To enter the amniotic cavity, an invasive procedure such as an amniocentesis must be performed. To measure the volume of AF, an inert dye must be injected, which dilutes to fill the amniotic cavity. Follow-up samples of amniotic fluid are then obtained to determine a dilution curve.⁹⁻¹⁵ Obviously, an amniocentesis has a small but real risk of interrupting the pregnancy, and any substance injected into the uterus can cause infection despite every precaution being taken.

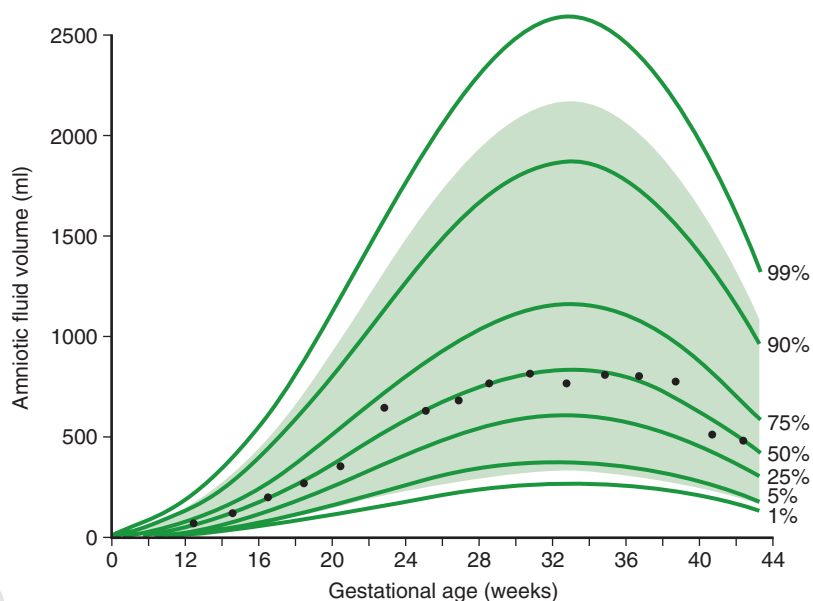


Figure 31-1. Nomogram showing amniotic fluid volume as a function of gestational age. The black dots are the mean for each 2-week interval. Percentiles calculated from polynomial regression equation and standard deviation of residuals. (Reproduced with permission from Brace RA, Wolf EJ: Normal amniotic fluid volume throughout pregnancy. *Am J Obstet Gynecol* 161:382, 1989.)

The dye injection technique is considered the “gold standard” for determining actual AFV and is compared with other methods of estimating AFV, such as ultrasound, discussed later in this chapter.

Despite these measurement limitations, Brace and Wolf identified all published measurements of AFV in 12 studies with 705 individual AFV measurements.¹⁶ Their findings are demonstrated in Figure 31-1. From this figure, it can be seen that for each week of gestation, there can be widely varying amounts of AF, which increase with advancing gestational age. The largest variation occurs at 32 to 33 weeks of gestation. At this time, the normal range (5th to 95th percent) is from 400 to 2100 ml. This represents a wide “normal range.” One of the most interesting findings of the Brace and Wolf study is that from 22 weeks through 39 weeks of gestation, the average volume of AF (black dots on Fig. 31-1) remained unchanged. At a time when the fetus weighed, on average, about 500 g at 22 weeks, up to term gestation when it weighed 3,500 g, a 7-fold increase in weight, the mean AFV was the same. This would suggest that AFV was being carefully regulated. This concept of fluid regulation is discussed later.

ULTRASOUND MEASUREMENTS OF AMNIOTIC FLUID VOLUME

Measuring true AFV is not only difficult but clinically impractical as well. Initial clinical assessments of AFV were through Leopold’s abdominal measurements, or measurement of the fundal height of the pregnant uterus. If the maternal uterus was large for gestational age, and the fetus could not be easily palpated, or was ballotable, it was believed that AFV was increased. More commonly, the diagnosis of polyhydramnios was made at the time of delivery when large volumes of AF rained down on the delivery room floor. The diagnosis of oligohydramnios

was considered when the fundal height was small for gestational age or the fetus could be easily palpated. Clearly, palpation as a method for determining AFV has its place, but the advent of ultrasound has afforded us the ability of looking, noninvasively, into the human uterus to examine both the fetus and AFV. Early ultrasound estimations of AFV were made by measuring the largest vertical pocket (LVP) of AF.¹⁷ Other researchers have examined the LVP, and then considered the horizontal plain, if the LVP was less than 1 cm.¹⁸ Chamberlain et al.¹⁸ and Mercer et al.¹⁹ found that with the LVP of AF less than 1 cm or 0.5 cm, respectively, perinatal morbidity and the PMR were increased. These lower values of the LVP certainly identified at-risk fetuses, but the sensitivity for identifying the majority of pregnancy complications associated with oligohydramnios, was not as strong, causing others to choose higher values as a cutoff point.

As the quality of ultrasound improved, investigators expanded their measurements to include the LVP in each of the four quadrants of the uterus throughout gestation. The uterus at any gestational age beyond 20 weeks is divided into four equal quadrants, as shown in Figure 31-2. The deepest clear pocket of AF is then measured, making sure that the ultrasound transducer is perpendicular to the floor. This four-quadrant measurement was termed the Amniotic Fluid Index (AFI) by Phelan et al. and has been described by others as well.²⁰⁻²² The clearest graphic presentation of the AFI (Fig. 31-3) is that of Moore and Cayle, who described their population of 791 normal pregnant women.²² Their cross-sectional study obtained only one AFI measurement from each pregnancy with a normal outcome.²² The 5th and 95th percentile of the AFI varied for each gestational age, suggesting that what may be normal for one gestational age period, may be abnormal for another. The 95th percentile for 35 to 36 weeks of gestation was a value of 24.9 cm, whereas the 95th percentile for 41 weeks of gestation was 19.4 cm. The variation in the AFI at the 5th percentile

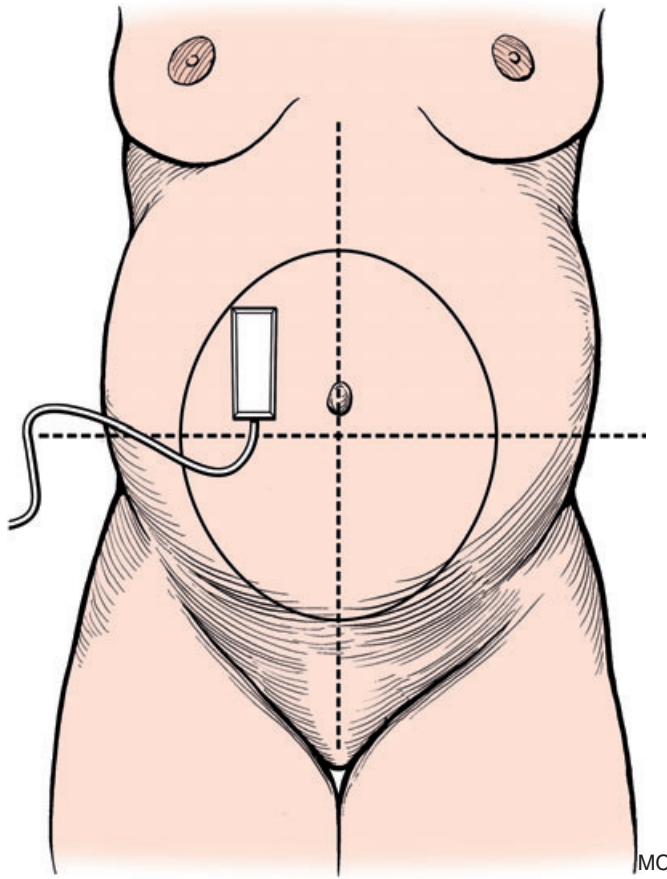


Figure 31-2. Schematic diagram of the technique for measuring the four-quadrant amniotic fluid index (AFI). (Reproduced with permission from Gilbert WM: Disorders of Amniotic Fluid. In Creasy RK, Resnik R [eds]: Maternal Fetal Medicine, 3rd ed. Philadelphia, W.B. Saunders. 1994, p 620.)

was less than that of the 95th percentile, but it still varied by as much as 2.5 cm. Finally, the investigators reported the interobserver and intraobserver variation to be 3.1 percent and 6.7 percent, respectively, which is acceptable for this commonly performed procedure.²² Comparing the ultrasound estimation of the AFV by the AFI (see Fig. 31-3) with the actual measured volume (see Fig. 31-1) demonstrates very similar-appearing curves.

Several authors have attempted to compare estimates of AFV by ultrasound (the LVP and the AFI) with actual measurement by the dye dilution technique, and report that the AFI does not predict actual AFV that well.⁹⁻²⁵ Dildy et al.²³ found that the AFI overestimated the actual volume in 88 percent of cases at lower volumes, and underestimated the actual volume in 54 percent of cases at higher volumes. The researchers went on to conclude that the difference between actual volume and estimated volume by the AFI should not change clinical practice.²³ Magann et al. have published several studies comparing the LVP with the AFI and dye dilution techniques, to determine which test is superior for predicting actual AFV, or perinatal morbidity or mortality.^{9,11-15,24-25} Consistently, they reported that both ultrasound methods

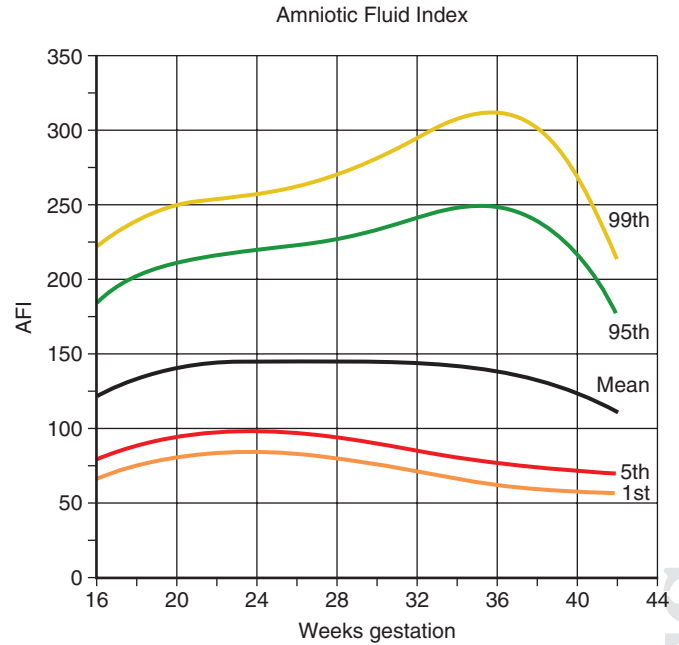


Figure 31-3. Amniotic fluid index (in millimeters) plotted with gestational age (weeks). The solid line denotes the 50th percentile; dashed lines, the 5th and 95th percentiles; and the dotted lines, + 2 standard deviations (2.5th and 97.5th percentiles). (Reproduced with permission from Moore TR, Cayle JE: The amniotic fluid index in normal human pregnancy. *Am J Obstet Gynecol.* 62:1168, 1990.)

(LVP and AFI) poorly predicted actual AFV. In addition, they found an observed sensitivity for an AFI measurement of less than 5 cm of 10 percent (specificity of 96 percent), whereas the LVP was worse (sensitivity 5 percent, specificity 98 percent).²⁵ When examining cases of suspected polyhydramnios, an AFI greater than 20 cm had a sensitivity of 29 percent (specificity 97 percent), which was equal to the LVP method (sensitivity of 29 percent, specificity of 94 percent). When the LVP method was compared with the AFI method, the former had fewer false-positive tests than the latter, suggesting the LVP was the superior method.²⁵ In comparison, Moore²⁶ found the AFI superior to the LVP for identifying cases of oligohydramnios but found the two methods similar at predicting polyhydramnios.

Measurement of the AFI can also vary widely depending upon the technique used. Flack et al.²⁷ reported that they could increase the AFI (13 percent) by using low pressure with the ultrasound transducer on the maternal abdomen, as compared with moderate pressure, or decrease the AFI (21 percent) with high pressure on the maternal abdomen. Clearly technique is important to prevent overestimating or underestimating the ultrasound measurement of the AFI. Despite the fact that the actual measurement of AFV by Brace and Wolf¹⁶ (see Fig. 31-1) roughly superimposes upon the graph of the normal AFI of Moore and Cayle²² (see Fig. 31-3), it does not mean that they will necessarily correlate well with each other.

4 Section V Complicated Pregnancy

For many years, investigators have tried, with mixed success, to demonstrate the utility and applicability of ultrasound estimation of AFV in relation to perinatal outcome. Early work by Chamberlain et al.¹⁸ found that with the LVP smaller than 1 cm, there was a marked increase in perinatal morbidity and mortality, which persisted even after correcting for birth defects. Despite overwhelming evidence that any ultrasound method for predicting AFV is poor at best, clinical practice continues to include the use of weekly or biweekly AFV estimation by ultrasound.

AMNIOTIC FLUID FORMATION

Fetal urine

The main source of AF is fetal urination. In the human, the fetal kidneys begin to make urine before the end of the first trimester, and production of urine continues from this point, ever increasing, until term gestation. Many different animal models have been used to study fetal urine production, with the fetal sheep being the most common.²⁸⁻³² The fetal sheep provides an excellent model for comparative human study owing to its similar fetal weight at term, its sufficient size allowing catheter placement, and the fact that the sheep fetus has a low risk of premature labor after catheter placement. In the fetal sheep, urine production has been reported to be approximately 200 to 1200 ml/day in the last third of pregnancy.^{28,32-33} Efforts to measure human fetal urine production have been accomplished by ultrasound measuring the change in fetal bladder volume over time. Wladimiroff and Campbell³⁴ initially measured three dimensions of the fetal bladder every 15 minutes and reported a human fetal urine production rate of 230 ml/day at 36 weeks of gestation, which increased to 655 ml/day at term. Others found similar volumes using the same technique.³⁵⁻³⁸ More recently, Rabinowitz et al.,³⁹ using the same technique as Wladimiroff and Campbell but measuring the change in volume every 2 to 5 minutes, found fetal urine production to be much greater than previously predicted, 1,224 ml/day. In Figure 31-4, the fetal urine production rates of several studies are shown, with the greatest volume being that of Rabinowitz et al., who measured at the most frequent intervals.³⁴⁻³⁹ Clearly, the human fetal urine production rate can be seen to be approximately 1000 to 1200 ml/day at term, suggesting that the entire AFV is replaced more frequently than every 24 hours.

Lung Liquid

Although rarely even contemplated by the practicing clinician, fetal lung liquid plays an important role in AF formation. For years, it was presumed that there was actual movement of AF into the fetal lungs under normal conditions; however, recent data offer no support this concept.^{40,41} In fact, there is normally an outward rather than inward movement of fluid from the lungs. Throughout gestation, the fetal lungs produce fluid that exits the

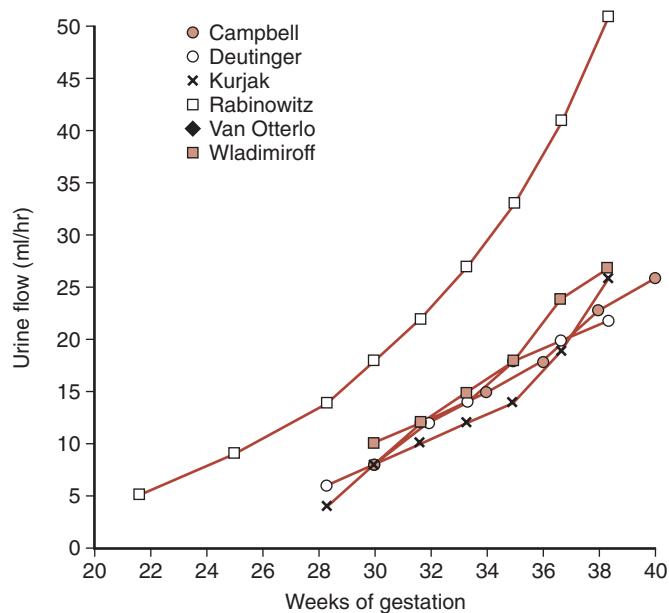


Figure 31-4. Normal changes in fetal urine flow rates across gestation. Lines represent mean values for six studies in the literature.³⁴⁻³⁹ The individual first authors are shown in the figure itself. The highest line is data from Rabinowitz et al and represents bladder volume measurements every 5 minutes instead of every 15 minutes, as is the case for the other five studies. (Reproduced with permission from Gilbert WM, Brace RA: Amniotic fluid volume and normal flows to and from the amniotic cavity. *Semin Perinatol* 7:150, 1993.)

trachea and is either swallowed, or leaves the mouth, and enters the amniotic compartment. Although never directly measured in humans, lung liquid values from the fetal sheep have provided some valuable data. In the fetal sheep, the lungs have been reported to produce volumes of up to 400 ml/day, with 50% being swallowed and 50% exiting via the mouth.^{31,42-45} In humans, we know that fetal lung liquid enters the amniotic compartment owing to the presence of surfactant within the AF, both near and at term, as measured by amniocentesis for lung maturity. During normal fetal life, the fetus performs breathing movements that provide a “to-and-fro” movement of AF into and out of the trachea, upper lungs and mouth.⁴⁶ Although AF may move back and forth, there is a net outward movement of fetal lung liquid. Clearly, the fetal lungs provide a volume of liquid to the AF, which adds to that of the fetal urine.

AMNIOTIC FLUID REMOVAL

Fetal Swallowing

In the human, fetal swallowing begins early in gestation. In the fetal sheep, swallowing has mostly been measured in the latter half of pregnancy and appears to increase with increasing gestational age. Sherman et al.⁴⁷ have reported that the ovine fetus swallows in episodes lasting 2 minutes and at volumes of 100 to 300 ml/kg/day. In the term ovine fetus, that volume represents a daily

swallowing rate of 350 to 1,000 ml/day for a 3.5 kg fetus. This is obviously more than the adult sheep, which drinks 40 to 60 ml/kg daily.⁴⁷

Many different techniques have been used to determine swallowing rates in the animal model, including repetitive sampling of injected dye and actual flow probe measurements.^{28,47} For obvious reasons, actual measurement of human fetal swallowing is much more difficult. In spite of this limitation, early studies in humans in the 1960s used fetuses that underwent injection of substances into the amniotic compartment to measure swallowing. Initial work was done by Pritchard in normal and anencephalic fetuses, and later by others in his laboratory.^{40,48} Human fetal swallowing was studied by injecting radioactive chromium-labeled erythrocytes and hypaque into the amniotic compartment, and swallowing rates of 72 to 262 ml/kg/day were found.^{40,48} Abramovich⁴⁹ injected colloidal gold into the human amniotic compartment and found that fetal swallowing increased with advancing gestational age. He also found similar swallowing rates to those reported by Pritchard.⁴⁹ Obviously similar studies could not be performed today, but the information is helpful in our understanding of human fetal swallowing. Clearly, fetal swallowing could not remove the entire volume of fluids entering the amniotic compartment from fetal urine production and lung liquid, and therefore, other mechanisms for AF removal must occur.

Intramembranous Absorption

One major stumbling block to the understanding of AFV regulation was the discrepancy between fetal urine and lung liquid production, and its removal by swallowing. Clearly something was missing in the equation. If the measurements and estimates of AF production and removal were accurate, there would be at least 500 to 750 ml/day entering the amniotic compartment, without leaving, which would result in acute polyhydramnios. This does not occur under normal conditions (see Fig. 31-1), clearly demonstrating the presence of other mechanisms that remove AF in order to maintain a normal volume. A second route for AF removal has been suggested, namely the intramembranous pathway.^{6-8,50-51} This process describes the movement of water and solutes between the amniotic compartment and the fetal blood, which circulates through the fetal surface of the placenta. The large osmotic gradient (Fig. 31-5) between AF and fetal blood provides a substantial driving force for the movement of AF into the fetal blood. This intramembranous absorption has been described in detail in the fetal sheep and also demonstrated to be present in the rhesus monkey fetus.^{6-8,50-51} Several anecdotal studies suggest that intramembranous absorption also occurs in humans. In separate publications, Heller⁵² and Renaud et al.⁵³ each injected labeled amnio acids into the amniotic compartments of women, who were shortly thereafter delivered by cesarean section. Both groups found high levels of the amino acids concentrated in the placenta within 45 minutes of injection. They concluded that the amino acids had to be absorbed by some route other than swallowing in order to explain the rapid absorption

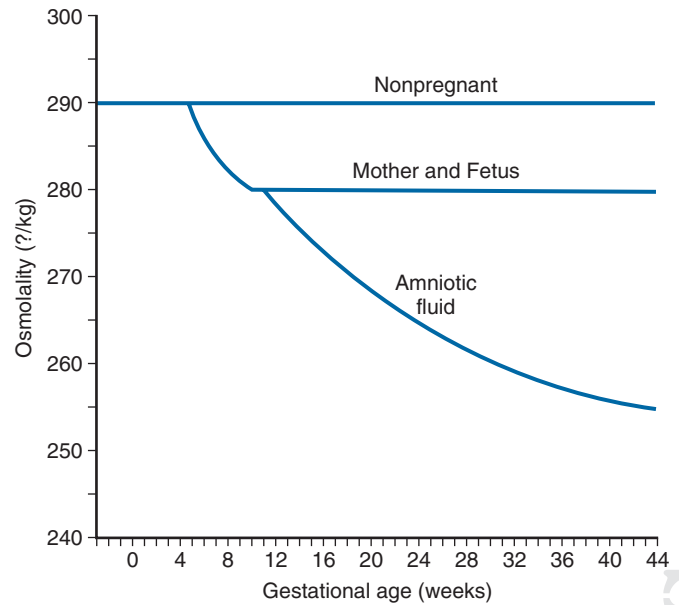


Figure 31-5. Change in maternal and fetal plasma and in amniotic fluid osmolality across gestation. (Reproduced with permission from Gilbert WM, Moore TR, Brace RA: Amniotic fluid volume dynamics. *Fetal Med Review* 3:89, 1991.)

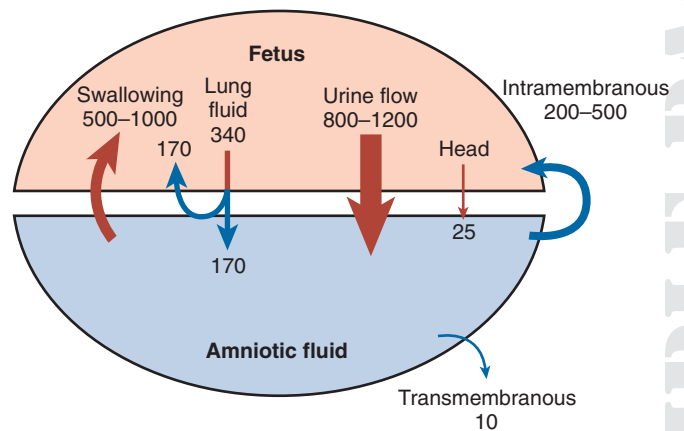


Figure 31-6. All known pathways for fluid and solute entry and exit from the amniotic fluid in the fetus near term. Arrow size is relative to associated flow rate. The solid arrows represent directly measured flows, whereas the hatched arrows represent estimated flows. The numbers represent volume flow in milliliters per day. The curved portion of the double arrow represents lung fluid that is directly swallowed after leaving the trachea, whereas the straight portion represents lung fluid that enters the amniotic cavity from the mouth and nose. (Reproduced with permission from Gilbert WM, Moore TR, Brace RA: Amniotic fluid volume dynamics. *Fetal Med Review* 3:89, 1991.)

into the fetal circulation within the placenta. Intramembranous absorption could easily explain this movement. This route of absorption is now being actively investigated, and researchers have noted that 200 to 500 ml/day leaves the amniotic compartment under normal physiologic conditions.^{6,7,54} In addition, it has been reported that absorption through the intramembranous pathway can increase almost 10-fold under experimental conditions in sheep.⁵⁵ Figure 31-6 demonstrates the summa-

tion of all currently identified avenues for fluid entry and exit from the amniotic compartment, along with their measured or estimated values. With the identification of intramembranous absorption as a significant route for the removal of amniotic water and solutes, it appears that all routes of entry and removal from the amniotic compartment have possibly been identified, and the equation of input and outflow has finally been balanced (Fig. 31-6). Recent work on the mechanisms associated with intramembranous absorption should help clarify this final chapter in our understanding of the normal physiology associated with AFV regulation.

OLIGOHYDRAMNIOS

In this section, we examine the association of oligohydramnios and perinatal outcome. The incidence of oligohydramnios varies depending on which definition is used, with a general reporting rate between 1 and 3 percent.⁵⁶ When women undergoing antepartum testing for high-risk pregnancy conditions are examined, the incidence of oligohydramnios is much higher (19 to 20 percent), as would be expected. This is primarily due to the underlying maternal or fetal indication for the antepartum testing.²⁵ Three studies have reported actual measured AFV but have reported somewhat different values for oligohydramnios: Brace and Wolf, less than 318 ml; Magann et al., less than 500 ml; and Horsager et al., less than 200 ml.^{9-10,16} With the advent of ultrasound estimation of AFV, multiple thresholds have been reported.^{3,17,57-59} An early publication by Chamberlain et al.¹⁸ reported a 50-fold increase in PMR for pregnancies with a LVP of less than 1 cm. This report was instrumental in raising concern about the risk of stillbirth and neonatal mortality in the presence of oligohydramnios. A second, less-often reported finding of that study was that 40 percent of the cases with oligohydramnios also had other confounding factors such as intrauterine growth restriction (IUGR), maternal hypertensive disorders, and congenital malformations.¹⁸ Clearly, oligohydramnios in the presence of IUGR, or preeclampsia, has markedly worse perinatal outcomes, but what are the risks in the cases of isolated oligohydramnios? Other investigators have reported that oligohydramnios in the prolonged pregnancy has an increased risk of meconium staining of the AF, fetal distress in labor, and low 1-minute Apgar scores.⁵⁶ A common clinical finding is the existence of a low AFI in an otherwise normal pregnancy, when an ultrasound is obtained for some other reason. Because the diagnosis of oligohydramnios has been associated with poor perinatal outcomes, many women, who are at or near term are sent to labor and delivery to be considered for induction, solely due to the low AFI. Frequently, their cervical examination is unfavorable for induction, and in spite of this, an induction is attempted. This can often result in a cesarean delivery for failed induction. Although the evidence for induction in the prolonged pregnancy is solid, the term or preterm patient with isolated oligohydramnios may not need immediate delivery.

Legrew et al.⁶⁰ reported that 41 percent of women with oligohydramnios, as determined by the AFI, had a normal AFI 3 to 4 days later. They also found that a normal AFI measurement was valid for 1 week, suggesting that the test need not be repeated more often than that, except in certain high-risk cases. Other studies have considered the question of isolated oligohydramnios and perinatal outcome. Magann et al.²⁵ examined 1,001 high-risk women undergoing antepartum testing. They found that those with an AFI of less than 5 cm (19 percent of cases) had similar outcomes to those with normal AFIs, and concluded that an AFI less than 5 cm was not an indication for delivery.²⁵ Rainford et al.⁶¹ examined 232 women who were greater than 37 weeks of gestation and who had an AFI less than 5 cm (19 percent). They found outcomes to be no worse when compared with those with a normal AFI. In fact, the risk of meconium staining of the AF was found to be increased (35 versus 16 percent) in the normal group.⁶¹ Finally, Casey et al.,⁵⁶ examining 6,423 women at greater than 34 weeks' gestation with an AFI less than 5 cm, found increases in intrauterine fetal death (IUFD), admissions to the neonatal intensive care unit (NICU), neonatal death, low birth weight, and meconium aspiration syndrome as compared with women with an AFI greater than 5 cm. If the birth defects and IUGR were removed, there was no difference in admissions to the NICU, neonatal death, or respiratory distress syndrome. This suggests that the IUGR and birth defects contributed to the increased morbidity and mortality, and not the oligohydramnios itself.

There is increasing evidence that patients with isolated oligohydramnios with a normally grown fetus, good fetal movement, and an unfavorable cervix may be candidates for observation or possible therapeutic intervention, or both, to increase the AF level. In subsequent sections of this chapter, we examine efforts to increase AFV.

Midgestation Oligohydramnios

It has been clearly established that when the AFV is greatly decreased, especially in midpregnancy, the perinatal mortality rate approaches 100 percent.¹⁻³ The cause of the decrease or absence of AF largely determines the perinatal outcome (Table 31-1). With renal agenesis, vir-

Table 31-1. Fetal and Maternal Causes of Oligohydramnios

Fetal conditions
Renal agenesis
Obstructed uropathy
Spontaneous rupture of the membranes (SROM)
Premature rupture of the membranes (PROM)
Abnormal placentation—elevated MSAFP/MSHCG
Prolonged pregnancy
Maternal conditions
Dehydration-hypovolemia
Hypertensive disorders
Uteroplacental insufficiency
Antiphospholipid syndrome
Idiopathic

MSAFP, maternal serum alpha fetoprotein; MSHCG, maternal serum human chorionic gonadotropin.

tually 100 percent of newborns die due to pulmonary hypoplasia. AF is required during certain periods of early and midgestation for fetal lung development, and without it, the lungs do not develop. If premature rupture of the membranes (PROM) results in a loss of all AF, perinatal outcome will vary based on during which period of gestation the membrane rupture occurred, and whether or not intraamniotic infection was the cause of the membrane rupture.⁶² Oligohydramnios can occur with hypertensive disorders or the antiphospholipid syndrome. In these cases, if the fetus is large enough for survival outside of the uterus, there may be little impact on perinatal outcome other than the consequences of prematurity.⁶²

Evaluation and Work-Up of Midgestation Oligohydramnios

When the diagnosis of oligohydramnios is made in the second trimester, it is vitally important to obtain a complete history and physical from the patient, as well as a targeted ultrasound. The patient should be questioned for any history consistent with rupture of the membranes, leakage of bloody fluid, or wetness of her underwear. If there is a question of the possible rupture of the membranes, a sterile speculum examination should be performed in an attempt to obtain fluid that can be examined for evidence of rupture. Specific tests include examining for microscopic ferning, checking for a neutral pH on nitrazine paper, and looking for pooling in the posterior vagina. When ferning is present, the sodium chloride concentration is high enough for crystallization or ferning to occur. The sodium chloride concentration of the AF is sufficient to cause ferning, whereas vaginal secretions usually do not fern. Determining the pH of the vaginal fluid can identify the neutral pH of AF as different from the acidic pH of normal vaginal secretions. Next, a targeted ultrasound should be performed to examine for the amount of AF present, the presence of normal anatomy including fetal kidneys and bladder, and finally, for appropriate interval growth. If the fetus is normally grown with kidneys and bladder visualized, more often than not, the fetal membranes have been prematurely ruptured. If kidneys and bladder cannot be seen, then the diagnosis is most likely renal agenesis. The difference between the prognosis of these two entities is dramatic. Renal agenesis is uniformly fatal, whereas PROM can have a reasonable prognosis if it occurs after fetal viability and if infection is not present.

Third-Trimester oligohydramnios

Although severe oligohydramnios has an increased PMR later in the third trimester, it is still not as high as earlier in pregnancy.^{3,56,63} Chamberlain et al.¹⁸ reported a 50-fold increase in PMR when the LVP of AF was less than 1 cm. This data has led many clinicians to induce or deliver women with oligohydramnios, even when there were no other indications for delivery (see discussion

above). The Chamberlain et al. study was problematic in that approximately 40 percent of the patients also had IUGR or hypertensive disorders, or both.¹⁸ This could easily explain the increase in mortality.¹⁸ Other studies have reported similar increases in perinatal mortality associated with oligohydramnios, but most have not corrected for other underlying medical conditions.¹⁷ When oligohydramnios is diagnosed in the prolonged pregnancy, there is an increased risk of meconium staining of the AF, meconium aspiration syndrome, fetal distress in labor, and increased cesarean delivery rates.^{59,64-65} For these reasons, induction of labor is indicated with oligohydramnios in the prolonged pregnancy. An important question currently under investigation is whether or not a patient with isolated oligohydramnios will have a worse pregnancy outcome if decreased AFV is the only finding. Because induction is indicated for oligohydramnios in the post-date period, many clinicians believe that induction is indicated for oligohydramnios at or close to term.

POLYHYDRAMNIOS

With the increasing use of real-time ultrasound, the diagnosis of polyhydramnios has been on the rise. Previously, the diagnosis of polyhydramnios was made when the uterus was large for gestational age or the fetus could not be easily palpated by Leopold's maneuvers. The diagnosis was often not made until the time of delivery, when large gushes of AF preceded or followed the delivery of the newborn. Polyhydramnios has an impact on perinatal morbidity and mortality based largely on the amount of fluid present, and when in gestation it presents. The earlier in gestation it occurs and the greater the amount of fluid, the higher the morbidity and mortality.⁴ The incidence of polyhydramnios has been reported to be about 1 percent in large population-based studies.⁶⁶⁻⁶⁹ The most common cause for severe polyhydramnios in midgestation is congenital malformations, with or without aneuploidy, and monozygotic twins.⁶⁸ Table 31-2 lists maternal and fetal causes of polyhydramnios, including congenital anomalies.

Table 31-2. Fetal and Maternal Causes of Polyhydramnios

Fetal conditions
Congenital Anomalies
Gastrointestinal obstruction
CNS abnormalities
Cystic hygromas
Nonimmune hydrops
Sacrococcygeal teratoma
Aneuploidy
Twin-to-twin transfusion syndrome
Muscular dystrophy syndromes
Maternal conditions
Idiopathic
Poorly controlled diabetes mellitus

CNS, central nervous system.

Early ultrasound studies examining polyhydramnios used the LVP method for measuring AFV. Most authors report an LVP of greater than 8 cm to define polyhydramnios.⁶⁸ Hill et al. divided their patients with polyhydramnios into three groups: mild (LVP 8 to 11 cm, 79 percent of cases), moderate (LVP 12 to 15 cm, 16.5 percent cases), and severe (LVP 16+cm, 5 percent of cases). Overall the perinatal mortality rate was 127.5/1,000, which corrected to 58.8/1,000 when lethal malformations were removed.⁶⁸ This value is markedly increased over the background rate. Hill et al. found that with mild polyhydramnios, a specific diagnosis for the cause of polyhydramnios could only be found 16 percent of the time.⁶⁸ This diagnosis increased to a rate of 90 percent for moderate polyhydramnios, and 100 percent for severe polyhydramnios.⁶⁸ In a follow-up study, Many et al.⁷⁰ examined 275 women with polyhydramnios to determine if the degree of polyhydramnios had an impact on the rate of prematurity. Although excessive amniotic fluid did not impact the rate of prematurity, the presence of anomalies or diabetes mellitus was associated with an increased risk of preterm delivery.⁷⁰

Later in pregnancy, with milder degrees of polyhydramnios, the cause is usually idiopathic or related to diabetes.⁶⁸⁻⁷² At present, there are no uniformly accepted criteria for making the diagnosis of polyhydramnios. Brace and Wolf¹⁶ defined polyhydramnios as being present when the actual fluid volume was greater than 2,100 ml (2.5 percent incidence), but an actual measurement of AFV is difficult and clinically impractical.

Using the four-quadrant AFI, Moore and Cayle²² reported the AFI for varying gestational ages (see Fig. 31-3) and concluded that one value for the AFI cannot be used throughout gestation but must be referenced to gestational age. The study found the 97.5 percentile at 35 weeks of gestation to be 27.9 cm, which represents the upper limits of normal for that gestational age. This value would clearly be abnormally increased for earlier and later measurements in gestation (see Fig. 31-3).

Midgestation Polyhydramnios

The pregnant woman who presents with a rapidly enlarging uterus in midpregnancy, or who presents in preterm labor, will most likely have a fetus with a congenital malformation or aneuploidy, or both.⁶⁸ Severe polyhydramnios in the second trimester has a significant PMR, which is most commonly due to prematurity or aneuploidy.^{73,74} The more common congenital malformations associated with severe polyhydramnios include the host of defects associated with gastrointestinal obstruction. Esophageal atresia with or without tracheoesophageal fistula can present with early-onset severe polyhydramnios owing to the blockage of fetal swallowing. With certain malformations, AFV may still be normal because a tracheoesophageal fistula, for example, provides for the movement of fluid into the stomach, and thus, polyhydramnios may not develop.⁷⁵ Other gastrointestinal obstructions such as duodenal atresia may result in polyhydramnios.⁶⁸ Whenever a structural defect is seen

in a fetus, consideration should be given to performing a karyotype owing to the dramatic increase in aneuploidy seen with one or more structural defects. Knowing the karyotype of the fetus with a defect may allow for further treatment options, or possible pregnancy termination. The fetus with polyhydramnios and trisomy 18 would be a candidate for pregnancy termination at any point in the pregnancy owing to the lethal nature of trisomy 18.

Another common cause of acute, severe, polyhydramnios in the second trimester is the condition associated with the twin-to-twin transfusion syndrome (TTS). This may be found in single placentas, monozygotic twin pregnancies. With identical twins who share a single placenta, 90 percent of the fetuses will have vascular connections between the arteries and veins on the surface of the placenta.⁷⁶ The most common connection is the artery-to-artery connection, followed by the vein-to-vein connection. The least common connection is the artery of one twin connecting to the vein of the other. This can lead to oligohydramnios of the twin with the arterial connection, and polyhydramnios in the twin with the venous connection. If the polyhydramnios/oligohydramnios is severe enough, the PMR can approach 100 percent without treatment. However, survival improves to 50 to 70 percent with intervention.^{4,5} Intervention in TTS is discussed later in the chapter under therapies for polyhydramnios and in Chapter 28.

Third-Trimester Polyhydramnios

When polyhydramnios occurs in the third trimester of pregnancy, it is usually mild and not associated with a structural defect.⁶⁸ Table 31-2 lists many of the causes of polyhydramnios. Despite the fact that a diagnosis can be determined for the majority of early-onset cases, for the vast majority of cases in the third trimester, a diagnosis cannot be found. Thus, these cases are given the diagnosis of idiopathic. Despite this, however, the other causes of polyhydramnios must be ruled out before the idiopathic label can be applied.

In many cases, polyhydramnios may be transient. Golan et al.⁶⁹ examined 113 cases of polyhydramnios. On repeated examination, patients separated into two groups: Those cases in which the polyhydramnios worsened or the AFV remained markedly elevated, and those whose AFV returned to normal, or decreased to mild polyhydramnios.⁶⁹ In the former group, all complications of pregnancy were greater, including preterm delivery (2.7-fold increase), preeclampsia (2.7-fold increase), IUDF (7.7-fold increase), and neonatal demise (7.7-fold increase). In the latter group in which the polyhydramnios improved or AFV returned to normal, the most common diagnosis was idiopathic and showed a favorable outcome.⁶⁹ This study would suggest that if polyhydramnios is persistent, the fetus should be examined closely for congenital malformations and aneuploidy, and monitored to prevent an IUDF. In addition, the mother should be watched closely for other medical complications of pregnancy.⁶⁹

Treatment of Oligohydramnios

Because of the increase in perinatal morbidity and mortality associated with oligohydramnios in the prolonged pregnancy, most authors recommend delivery in these cases. As discussed earlier, however, the patient who presents with isolated oligohydramnios in the third trimester may be a candidate for continued observation.^{25,56,61} Several investigators have attempted to treat oligohydramnios with the oral administration of water in the hope of “hydrating” the fetus through the mother. Animal studies have demonstrated that there is a close relationship between the hydration or dehydration of the mother and the fetus.^{77,78} Attempts to dehydrate the mother have resulted in dehydration of the fetus, and in some cases vice versa. In human pregnancies, Goodlin et al.⁷⁹ found that the maternal intravascular volume was low in cases of idiopathic oligohydramnios, and that by increasing the intravascular volume, the oligohydramnios resolved. In their initial study of the use of oral hydration as a treatment for women with a low AFI, Kilpatrick et al.⁸⁰ randomized women into two groups: The treatment group was told to drink 2 liters of water within 4 hours of a repeat AFI, and a control group that did not drink the 2 liters of water.

The treatment group had a significantly greater increase in AFI on repeat testing (6.3 cm) than the control group (5.1 cm).⁸⁰ They concluded that the oral administration of water could increase the AFI in women with oligohydramnios.⁸⁰ A follow-up study by the same group observed that women with normal AFV could increase or decrease their AFI depending upon the amount of water the mothers drank.⁸¹ As demonstrated in Table 31-3, the AFI significantly increased in the oral hydration group as compared with the control group. The control group was given what was thought to be a “normal” volume of water to drink, but as can be seen from Table 31-3, the AFI actually decreased and urine osmolality increased. This suggests that the mothers were actually dehydrated during the control portion of the study. Both groups demonstrated that the AFI can be influenced by increasing or decreasing water intake orally.

Table 31-3. Change in Amniotic Fluid Index 4–6 hours After Oral Water Hydration

	CONTROL (N = 20)	HYDRATION (N = 20)
Pretreatment		
AFI (cm)	17.7 ± 5.0	18.4 ± 4.7
USG	1.013 + 0.007	1.015 + 0.008
Post treatment		
AFI (cm)	16.2 ± 4.5*	21.4 ± 4.5#
USG	1.019 ± 0.009#	1.006 ± 0.006#
Delta AFI (cm)	-1.5 ± 2.7	3.0 ± 2.4
Intake (ml)	1576 + 607	1596 + 465

AFI, Amniotic fluid index; USG, urine specific gravity; Delta AFI, change in AFI from pre- to posttreatment. *, $P < 0.02$, paired t test, pre vs post treatment, #, $P < 0.0001$, paired t test pre vs post treatment. Intake, amount of fluid intake over the previous 24 hours other than the 2 liters.

From Kilpatrick SJ, Safford KL. Maternal hydration increases amniotic fluid index in women with normal amniotic fluid. *Obstet Gynecol* 81:50, 1993.

Many other studies have shown a similar improvement in AFV with either oral or intravenous administration of water and/or crystalloids.^{82,83} Several researchers have reported success in improving AFV in women with oligohydramnios by the injection of a crystalloid solution into the amniotic compartment during an amniocentesis.⁸⁴ The injection of fluid also allows for a more complete ultrasound examination of the fetus, which previously was not available owing to the lack of AF. Most of these studies, however, have been case reports, and because no large prospective studies have been performed, the routine use of amniocentesis for cases of marked oligohydramnios in midgestation cannot be justified by the literature.

Oligohydramnios in Labor

Almost 30 years ago, Gabbe et al.⁸⁵ working with fetal monkeys, noted that when AF was removed from the amniotic compartment, variable decelerations in the fetal heart rate developed. These decelerations resolved when the AF was replaced, suggesting that cord compression was the cause of the decelerations. Since that time, multiple investigators have studied amnioinfusion as a technique by which to treat variable decelerations in labor. Although most report a decrease in the frequency of variable decelerations, few have demonstrated any decrease in perinatal morbidity or mortality, or the cesarean delivery rate.^{86–90} Amnioinfusion has been studied as a possible therapy in the case of thick meconium. In several prospective studies, it has been shown to improve neonatal outcomes, including meconium visualized below the newborn vocal cords, and meconium aspiration syndrome.^{91–94} Sadovsky et al.⁹⁴ found that with the randomization of women with greater than light meconium to a control or amnioinfusion treatment group, 29 percent of control newborns had meconium below the umbilical cords, whereas none of the treated newborns did. Two meta-analyses that examined the therapeutic use of amnioinfusion for thick meconium demonstrated between a 75 and 84 percent reduction in meconium below the vocal cords at delivery, confirming that it should be offered to women who present with thick meconium.^{95,96} Of note, a recent, multicenter, randomized trial of 1,998 women in labor at 36 weeks' gestation or later with thick meconium did not find that amnioinfusion reduced the risk of moderate or severe meconium aspiration syndrome or perinatal death.⁹⁷ The authors concluded that amnioinfusion should not be recommended to prevent meconium aspiration syndrome.

Treatment of Polyhydramnios

Treatment options for patients with polyhydramnios are usually tailored to the underlying cause of the polyhydramnios. With mild idiopathic polyhydramnios, in which the work-up is negative, and follow-up ultrasound demonstrates persistent polyhydramnios, the only possible intervention might be antepartum testing with fetal kick counts, or nonstress tests. When poorly controlled

diabetes mellitus is the cause of the polyhydramnios, proper glycemic control may be beneficial as a treatment option.^{71,72} With the current aggressive management of diabetes in pregnancy, it is rare to see severe polyhydramnios associated with diabetes. Usually, if the diabetes is not well controlled, then the mother will undergo antepartum testing to assess fetal well-being.

Polyhydramnios associated with a fetal structural abnormality such as an obstruction to swallowing, usually requires invasive testing by amniocentesis to rule out aneuploidy. Often, the degree of polyhydramnios in these cases is severe and the resulting overdistention of the uterus causes preterm labor long before the due date. In these cases, one medical treatment option involves the administration of a prostaglandin inhibitor such as indomethacin, which works by decreasing fetal urine production.⁹⁸⁻¹⁰⁰ Prostaglandin inhibitors have been shown to decrease fetal urine output significantly. This effect occurs within 5 hours of starting the medication and decrease AFV within 24 hours.^{98,99} Although indomethacin has been shown to be relatively safe when given over a short period of time, such as 72 hours, prolonged usage may be associated with risks to the fetus. Prolonged use has been shown to cause premature closure, or narrowing, of the ductus venosus within the fetal heart and renal abnormalities in the newborn period.^{97,100} Complications related to indomethacin use worsen with advancing gestational age, and such treatment beyond 31 to 32 weeks of gestation should be avoided.¹⁰¹ Because of the adverse effects on the fetus associated with the long-term use of indomethacin, it probably has limited use in pregnancy for the treatment of severe polyhydramnios.

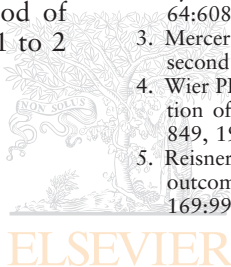
For those pregnancies complicated by the TTS, or for the fetus with obstructed swallowing, repetitive amnioreductions may be required to reduce the AFV until the fetus reaches viability.^{5,101,102} Severe cases of TTS, if left untreated, can have a PMR approaching 100 percent. Repetitive amnioreductions, in which an amniocentesis is performed and AF is withdrawn until the AFI is normal, can reduce the PMR from 100 percent to about 50 percent.^{5,102,103} Further options for the treatment of the TTS include the ablation of the connecting blood vessels by laser photocoagulation via fetoscopy.¹⁰⁴ A recent large prospective trial found that the laser ablation of the connecting blood vessels resulted in better outcomes for the twin pregnancy as compared with amnioreduction alone.¹⁰⁵ A major problem with laser ablation is that only certain centers perform the procedure, and most insurance companies will not pay for the procedure. This is not the case with amnioreductions, which can be performed anywhere and, therefore, are usually covered by insurance. Although laser ablation treatment may “cure” the cause of the TTS, amnioreduction only treats the symptoms. As a result, the amnioreduction method of treatment may require repeated procedures every 1 to 2 weeks for the remainder of the pregnancy.

KEY POINTS

- Amniotic fluid is seldom considered important until polyhydramnios or oligohydramnios occurs, either of which may significantly impact perinatal survival.
- Amniotic fluid is dynamic, with large volume flows into and out of the amniotic compartment each day.
- Clinical estimates of actual amniotic fluid volume through ultrasound measurements of the AFI or LVP are not very accurate at predicting true volume.
- Oligohydramnios, when associated with IUGR or prolonged gestations, is associated with significant increases in perinatal morbidity and mortality.
- Preterm or term isolated oligohydramnios, with an otherwise normal fetus, is not associated with an increase in perinatal morbidity or mortality.
- Early-onset or severe polyhydramnios is associated with a significant increase in aneuploidy, congenital malformations, preterm delivery, and perinatal mortality.
- The cause of mild polyhydramnios, especially in the latter part of the third trimester, is usually idiopathic, or related to diabetes mellitus, and has little positive or negative impact on perinatal survival.
- Amniotic fluid volume as estimated by the amniotic fluid index, can be increased or decreased by the amount of water ingested orally.
- Indomethacin, which decreases fetal renal and possibly pulmonary fluid production, can decrease AFV over time when taken orally.
- Absorption of amniotic fluid directly from the amniotic compartment into the blood vessels on the fetal surface of the placenta can explain the large differences between fetal swallowing and urine production.

REFERENCES

1. Hackett GA, Nicolaidis KH, Campbell S: The value of Doppler ultrasound assessment of fetal and uteroplacental circulations when severe oligohydramnios complicates the second trimester of pregnancy. *Br J Obstet Gynaecol* 94:1074, 1987.
2. Barss VA, Benacerraf BR, Frigoletto FD: Second trimester oligohydramnios, a predictor of poor fetal outcome. *Obstet Gynecol* 64:608, 1984.
3. Mercer LJ, Brown LG: Fetal outcome with oligohydramnios in the second trimester. *Obstet Gynecol* 67:840, 1986.
4. Wier PE, Raten G, Beisher N: Acute polyhydramnios- a complication of monozygous twin pregnancy. *Br J Obstet Gynaecol* 86: 849, 1979.
5. Reisner DP, Mahony BS, Petty CN, et al: Stuck twin syndrome: outcome in thirty-seven consecutive cases. *Am J Obstet Gynecol* 169:991, 1993.



6. Gilbert WM, Brace RA: The missing link in amniotic fluid volume regulation: Intramembranous absorption. *Obstet Gynecol* 74:748, 1989.
7. Gilbert WM, Brace RA: Novel determination of filtration coefficient of ovine placenta and intramembranous pathway. *Am J Physiol* 259:R1281, 1990.
8. Gilbert WM, Cheung CY, Brace RA: Rapid intramembranous absorption into the fetal circulation of arginine vasopressin injected intraamniotically. *Am J Obstet Gynecol* 164:1013, 1991.
9. Magann EF, Nolan TE, Hess LW, et al: Measurement of amniotic fluid volume: accuracy of ultrasonography techniques. *Am J Obstet Gynecol* 167:1533, 1992.
10. Horsager R, Nathan L, Leveno KJ: Correlation of measured amniotic fluid volume and sonographic predictions of oligohydramnios. *Obstet Gynecol* 83:955, 1994.
11. Magann EF, Bass JD, Chauhan SP, et al: Amniotic fluid volume in normal singleton pregnancies. *Obstet Gynecol* 90:524, 1997.
12. Magann EF, Doherty DA, Field K, et al: Biophysical profile with amniotic fluid volume assessments. *Obstet Gynecol*. 104:5, 2004. Comment in: *Obstet Gynecol* 104:3, 2004.
13. Magann EF, Doherty DA, Chauhan SP, et al: Dye-determined amniotic fluid volume and intrapartum/neonatal outcome. *J Perinatol* 24:423, 2004.
14. Magann EF, Doherty DA, Chauhan SP, et al: How well do the amniotic fluid index and single deepest pocket indices (below the 3rd and 5th and above the 95th and 97th percentiles) predict oligohydramnios and hydramnios? *Am J Obstet Gynecol*. 190:164, 2004.
15. Magann EF, Doherty DA, Chauhan SP, et al: Is there a relationship to dye determined or ultrasound estimated amniotic fluid volume adjusted percentiles and fetal weight adjusted percentiles? *Am J Obstet Gynecol*. 190:1610, 2004.
16. Brace RA, Wolf EJ: Characterization of normal gestational changes amniotic fluid volume. *Am J Obstet Gynecol* 161:382, 1989.
17. Manning FA, Hill LM, Platt LD: Qualitative amniotic fluid volume determination by ultrasound: antepartum detection of intrauterine growth retardation. *Am J Obstet Gynecol* 139:254, 1981.
18. Chamberlain PF, Manning FA, Morrison I, et al: Ultrasound evaluation of amniotic fluid volume. I: The relationship of marginal and decreased amniotic fluid volumes to perinatal outcome. *Am J Obstet Gynecol* 150:245, 1984.
19. Mercer LJ, Brown LG, Petres RE, et al: A survey of pregnancies complicated by decreased amniotic fluid. *Am J Obstet Gynecol* 149:355, 1984.
20. Phelan JP, Ohn MO, Smith CV, et al: Amniotic fluid index measurements during pregnancy. *J Reprod Med* 32:603, 1987.
21. Rutherford SE, Phelan JP, Smith CV, et al: The four quadrant assessment of amniotic fluid volume: an adjunct to antepartum fetal heart rate testing. *Obstet Gynecol* 70:353, 1987.
22. Moore TR, Cayle JE: The amniotic fluid index in normal human pregnancy. *Am J Obstet Gynecol* 162:1168, 1990.
23. Dildy GA III, Lira N, Moise KJ, et al: Amniotic fluid volume assessment: comparison of ultrasonographic estimates versus direct measurements with a dye-dilution technique in human pregnancies. *Am J Obstet Gynecol* 167:986, 1992.
24. Magann EF, Doherty DA, Chauhan SP, et al: Effect of maternal hydration on amniotic fluid volume. *Obstet Gynecol* 101:1261, 2003.
25. Magann EF, Chauhan SP, Barrilleaux PS, et al: Amniotic fluid index and single deepest pocket: Weak indicators of abnormal amniotic volumes. *Obstet Gynecol* 96:737, 2000.
26. Moore TR: Superiority of the four-quadrant sum over the single-deepest-pocket technique in ultrasonographic identification of abnormal amniotic fluid volumes. *Am J Obstet Gynecol* 163:762, 1990.
27. Flack NJ, Dore C, Southwell D, et al: The influence of operator transducer pressure on ultrasonographic measurements of amniotic fluid volume. *Am J Obstet Gynecol* 171:218, 1994.
28. Tomoda S, Brace RA, Longo L: Amniotic fluid volume and fetal swallowing rate in sheep. *Am J Physiol* 249:R133, 1985.
29. Alexander DP, Nixon DA, Widdas WF, et al: Gestational variations in the composition in the foetal fluids and foetal urine in the sheep. *J Physiol* 140:1, 1958
30. 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* 227:503, 1972
31. Adamson TM, Brodecky V, Lambert TF, et al: The production and composition of lung liquids in the in-utero foetal lamb. *In* •• (eds): *Foetal and Neonatal Physiology*. Cambridge, UK, Cambridge University Press, 1973, p 208. 3
32. Gresham EL, Rankin JHG, Makowski EL, et al: An evaluation of fetal renal function in a chronic sheep preparation. *J Clin Invest* 51:149, 1972.
33. Wintour EM, Barnes A, Brown EH, et al: Regulation of amniotic fluid volume and composition on the ovine fetus. *Obstet Gynecol* 52:689, 1978.
34. Wladimiroff JW, Campbell S: Fetal urine-production rates in normal and complicated pregnancy. *Lancet* 1:151, 1974.
35. Campbell S, Wladimiroff JW, Dewhurst CJ: The antenatal measurement of fetal urine production. *J Obstet Gynaecol Br Commonw* 80:680, 1973.
36. Van Otterlo LC, Wladimiroff JW, Wallenburg HCS: Relationship between fetal urine production and amniotic fluid volume in normal pregnancy and pregnancy complicated by diabetes. *Br J Obstet Gynaecol* 84:205, 1977.
37. Kurjak A, Kirkinsen P, Latin V, et al: Ultrasonic assessment of fetal kidney function in normal and complicated pregnancies. *Am J Obstet Gynecol* 141:266, 1981.
38. Deutinger J, Bartl W, Pfersmann C, et al: Fetal Kidney volume and urine production in cases of fetal growth retardation. *J Perinat Med* 15:307, 1987.
39. Rabinowitz R, Peters MT, Vyas S, et al: Measurement of fetal urine production in normal pregnancy by real-time ultrasonography. *Am J Obstet Gynecol* 161:1264, 1989.
40. Duenhoelter JH, Pritchard JA. Fetal respiration: quantitative measurements of amniotic fluid inspired near term by human and rhesus fetuses. *Am J Obstet Gynecol* 125: 306, 1976.
41. Seeds AE. Current concepts of amniotic fluid dynamics. *Am J Obstet Gynecol* 138: 575, 1980.
42. Mescher EJ, Platzker A, Ballard PL, et al: Ontogeny of tracheal fluid, pulmonary surfactant, and plasma corticoids in the fetal lamb. *J Appl Physiol* 39:1017, 1975.
43. Olver RE, Strang LB: Ion fluxes across the pulmonary epithelium and the secretion of lung liquid in the foetal lamb. *J Physiol* 241:327, 1974.
44. Lawson EE, Brown ER, Torday JS, et al: The effect of epinephrine on tracheal fluid flow and surfactant efflux in fetal sheep. *Am Rev Respir Dis* 118:1023, 1978.
45. Brace RA, Wlodek ME, Cook ML, et al: Swallowing of lung liquid and amniotic fluid by the ovine fetus under normoxic and hypoxic conditions. *Am J Obstet Gynecol* 171:764, 1994.
46. Patrick J, Campbell K, Carmichael L, et al: Patterns of human fetal breathing at 30–31 and 38–39 weeks' gestational age. *Obstet Gynecol* 56:24, 1980.
47. Sherman DJ, Ross MG, Day L, et al: Fetal Swallowing: correlation of electromyography and esophageal fluid flow. *Am J Physiol* 258:R1386, 1990.
48. Prichard JA: Deglutition by normal and anencephalic fetuses. *Obstet Gynecol* 25:289, 1965.
49. Abramovich DR: Fetal Factors influencing the volume and composition of liquor amnii. *J Obstet Gynaecol Britt Commw* 77:865, 1970.
50. Gilbert WM, Moore TR, Brace RA: Amniotic fluid volume dynamics. *Fetal Med Rev* 3:89, 1991.
51. Gilbert WM, Eby-Wilkens EM, Tarantal AF: The missing-link in Rhesus monkey amniotic fluid volume regulation: Intramembranous absorption. *Obstet Gynecol* 892:462, 1997.
52. Heller L: Intrauterine amino acid feeding of the fetus. *In* Bode H, Warshaw J (eds): *Parenteral Nutrition in Infancy and Childhood*. New York, NY, Plenum Press, 1974, p 206.
53. Renaud R, Kirschtetter L, Koehl D, et al: Amino-acid intra-amniotic injections. *In* Persianinov LS, Chervakova TV, Presl J (eds): *Recent Progress in Obstetrics and Gynaecology*. Amsterdam, Excerpta Medica, 1974, p 234.
54. Jang PR, Brace RA: Amniotic fluid composition changes during urine drainage and tracheoesophageal occlusion in fetal sheep. *Am J Obstet Gynecol* 167:1732, 1992.
55. Faber JJ, Anderson DF: Absorption of amniotic fluid by amniochorion in sheep. *Am J Physiol* 282:H850, 2002.

56. Casey BM, McIntire DD, Bloom SL, et al: Pregnancy outcomes after antepartum diagnosis of oligohydramnios at or beyond 34 weeks' gestation. *Am J Obstet Gynecol* 182:909, 2000.
57. Manning FA, Harmon CR, Morrison I, et al: Fetal assessment based on fetal biophysical profile scoring. IV. An analysis of perinatal morbidity and mortality. *Am J Obstet Gynecol*. 162:703, 1990.
58. Halperin ME, Fong KW, Zalev AH, et al: Reliability of amniotic fluid volume estimation from ultrasonograms: intraobserver and interobserver variation before and after the establishment of criteria. *Am J Obstet Gynecol* 153:264, 1985.
59. Crowley P, O'Herlihy C, Boylan P: The value of ultrasound measurement of amniotic fluid volume in the management of prolonged pregnancies. *Br J Obstet Gynaecol*. 91:444, 1984.
60. Lagrew DC, Pircon RA, Nageotte M, et al: How frequently should the amniotic fluid index be repeated? *Am J Obstet Gynecol* 167:1129, 1992.
61. Rainford M, Adair R, Scialli AR, et al: Amniotic fluid index in the uncomplicated term pregnancy. Prediction of outcome. *J Reprod Med* 46:589, 2001.
62. Hill MH: Oligohydramnios: Sonographic Diagnosis and Clinical Implications. *Clin Obstet Gynecol*. 40:314, 1997.
63. Jeng CJ, Lee JF, Wang KG, et al: Decreased amniotic fluid index in term pregnancy. Clinical significance. *J Reprod Med* 37:789, 1992.
64. Chauhan SP: Amniotic fluid index before and after amnioinfusion of a fixed volume of normal saline. *J Reprod Med* 36:801, 1991.
65. Grubb DK, Paul RH: Amniotic fluid index and prolonged antepartum fetal heart rate decelerations. *Obstet Gynecol* 9:558, 1992.
66. Chamberlain PF, Manning FA, Morrison I, et al: Ultrasound evaluation of amniotic fluid volume II: The relationship of increased amniotic fluid volume to perinatal outcome. *Am J Obstet Gynecol* 150:250, 1984.
67. Biggio JR Jr, Wenstrom KD, Dubard MB, et al: Hydramnios prediction of adverse perinatal outcome. *Obstet Gynecol* 94:773, 1999.
68. Hill LM, Breckle R, Thomas ML, et al: Polyhydramnios: Ultrasonically detected prevalence and neonatal outcome. *Obstet Gynecol* 69:21, 1987.
69. Golan A, Wolman I, Sagi J, et al: Persistence of polyhydramnios during pregnancy-its significance and correlation with maternal and fetal complications. *Gynecol Obstet Invest*. 37:18, 1994.
70. Many A, Hill LM, Lazebnik N, et al: The association between polyhydramnios and preterm delivery. *Obstet Gynecol* 86:389, 1995.
71. Bartha JL, Martinez-Del-Fresno P, Comino-Delgado R: Early diagnosis of gestational diabetes mellitus and prevention of diabetes-related complications. *Eur J Obstet Gynecol Reprod Biol* 109:41, 2003.
72. Thomas A, Kaur S, Somville T: Abnormal glucose screening test followed by normal glucose tolerance test and pregnancy outcome. *Saudi Med J*. 23:814, 2002.
73. Pauer HU, Viereck V, Krauss V, et al: Incidence of fetal malformations in pregnancies complicated by oligo- and polyhydramnios. *Arch Gynecol Obstet* 268: 52, 2003.
74. Desmedt EJ, Henry OA, Beischer NA: Polyhydramnios and associated maternal and fetal complications in singleton pregnancies. *Br J Obstet Gynaecol* 97:1115, 1990.
75. Lloyd JR, Clatworthy HW: Hydramnios as aid to the early diagnosis of congenital obstruction of the alimentary tract: A Study of the maternal and fetal factors. *Pediatrics* June:903, 1958.
76. Benirschke K: Twin placenta in perinatal mortality. *NY State J Med* 61:1499, 1961.
77. Ross MG, Ervin MG, Leake RD, et al: Bulk flow of amniotic fluid water in response to maternal osmotic challenge. *Am J Obstet Gynecol* 147:697, 1983.
78. Woods LL: Fetal renal contribution to amniotic fluid osmolality during maternal hypertonicity. *Am J Physiol* 250:R235, 1986.
79. Goodlin RC, Anderson JC, Gallagher TF: Relationship between amniotic fluid volume and maternal plasma volume expansion. *Am J Obstet Gynecol* 146:505, 1983.
80. Kilpatrick SJ, Safford K, Pomeroy T, et al: Maternal hydration affects amniotic fluid index (AFI). *Am J Obstet Gynecol* 164:361, 1991.
81. Kilpatrick SJ, Safford KL: Maternal hydration increases amniotic fluid index in women with normal amniotic fluid volumes. *Obstet Gynecol* 81:49, 1993.
82. Flack NJ, Sepulveda W, Bower S, et al: Acute maternal hydration in third-trimester oligohydramnios: effects on amniotic fluid volume, uteroplacental perfusion, and fetal blood flow and urine output. *Am J Obstet Gynecol* 173:1186, 1996.
83. Doi S, Osada H, Seki K, et al: Effect of maternal hydration on oligohydramnios: a comparison of three volume expansion methods. *Obstet Gynecol* 92:525, 1998.
84. Sepulveda W, Flack NJ, Fisk NM: Direct volume measurement at midtrimester amnioinfusion in relation to ultrasonographic indexes of amniotic fluid volume. *Am J Obstet Gynecol* 170:1160, 1994.
85. Gabbe SG, Ettinger BB, Freeman RK, et al: Umbilical cord compression associated with amniotomy: laboratory observations. *Am J Obstet Gynecol* 126:353, 1976.
86. Nageotte MP, Bertucci L, Towers CV, et al: Prophylactic amnioinfusion in pregnancies complicated by oligohydramnios: a prospective study. *Obstet Gynecol* 77:677, 1991.
87. Ogundipe OA, Spong CY, Ross MG: Prophylactic amnioinfusion for oligohydramnios: A reevaluation. *Obstet Gynecol* 84:544, 1994.
88. Schrimmer DB, Macri CJ, Paul RH: Prophylactic amnioinfusion as a treatment for oligohydramnios I laboring patients: a prospective randomized trial. *Am J Obstet Gynecol* 165:972, 1991.
89. Miyazaki FS, Taylor NA: Saline amnioinfusion for relief of variable or prolonged decelerations. *Am J Obstet Gynecol* 146:670, 1983.
90. Chanhan SP, Rutherford SE, Hess LW, et al: Prophylactic intrapartum amnioinfusion for patients with oligohydramnios. *J Reprod Med* 37:817, 1992.
91. Wenstrom KD, Parsons MT: The prevention of meconium aspiration in labor using amnioinfusion. *Obstet Gynecol* 73:647, 1989.
92. Eriksen NL, Hostetter M, Parisi VM: Prophylactic amnioinfusion in pregnancies complicated by thick meconium. *Am J Obstet Gynecol* 171:1026, 1994.
93. Macri CJ, Schrimmer DB, Leung A, et al: Prophylactic amnioinfusion improves outcome of pregnancy complicated by thick meconium and oligohydramnios. *Am J Obstet Gynecol* 167:117, 1992.
94. Sadosky Y, Amon E, Bade ME, et al: Prophylactic amnioinfusion during labor complicated by meconium: A preliminary report. *Am J Obstet Gynecol* 161:613, 1989.
95. Glantz JC, Letteney DL: Pumps and warmers during amnioinfusion: Is either necessary? *Obstet Gynecol* 87:150, 1996.
96. Pierce J, Gaudier FL, Sanchez-Ramos L: Intrapartum amnioinfusion for meconium-stained fluid: Meta-analysis of prospective trials. *Obstet Gynecol* 95:1051, 2000.
97. Fraser WD, Hofmeyr J, Lede R, et al: Amnioinfusion for the prevention of the meconium aspiration syndrome. *N Engl J Med* 353:909, 2005.
98. Stevenson KM, Lumbers ER: Effects of indomethacin on fetal renal function, renal and umbilicoplacental blood flow and lung liquid production. *J Dev Physiol* 17:257, 1992.
99. Kirshon B, Moise KJ, Wasserstrum N, et al: Influence of short-term indomethacin therapy on fetal urine output. *Obstet Gynecol* 72:51, 1988.
100. Mamopoulos M, Assimakopoulos E, Reece EA, et al: Maternal indomethacin therapy in the treatment of polyhydramnios. *Am J Obstet Gynecol* 162:1225, 1990.
101. Moise KJ: Polyhydramnios. *Clin Obstet Gynecol* 40:266, 1997.
102. Elliott JP, Urig MA, Clewell WH: Aggressive therapeutic amniocentesis for treatment of twin-twin transfusion syndrome. *Obstet Gynecol* 77:537, 1991.
103. Dickinson JE: Severe twin-twin transfusion syndrome: Current management concepts. *Aust NZ J Obstet Gynaecol* 35:16, 1995.
104. De Lia JE, Cruikshank DP, Keye WR: Fetoscopic neodymium: yag laser occlusion of placental vessels in severe twin-twin transfusion syndrome. *Obstet Gynecol* 75: 1046, 1990.
105. Eurofetus trial.

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