

## Physiology of amniotic fluid volume regulation

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**INTRODUCTION** — Amniotic fluid (AF) is the liquid that surrounds the fetus after the first few weeks of gestation. During much of pregnancy, AF is derived almost entirely from the fetus and has a number of functions that are essential for normal growth and development [1]:

- It helps to protect the fetus from trauma to the maternal abdomen
- It cushions the umbilical cord from compression between the fetus and uterus
- It has antibacterial properties that provide some protection from infection
- It serves as a reservoir of fluid and nutrients for the fetus
- It provides the necessary fluid, space, and growth factors to permit normal development of the fetal lungs and musculoskeletal and gastrointestinal systems.

Aberrations in amniotic fluid volume (AFV), both low (oligohydramnios) and high (polyhydramnios), are associated with a multitude of pregnancy-related problems. As an example, one study examined the pregnancy outcome of 147 women with a sonographic diagnosis of oligohydramnios (AF index <5 cm) [2]. Compared to women with AF index >5 cm, these pregnancies had an increased incidence of labor induction (42 versus 18 percent), stillbirth (1.4 versus 0.3 percent), nonreassuring fetal heart rate (48 versus 39 percent), admission to the neonatal intensive care nursery (7 versus 2 percent), meconium aspiration syndrome (1 versus 0.1 percent), and neonatal death (5 versus 0.3 percent). Another report assessed the adverse effects of persistent polyhydramnios in 65 women [3]. The women had increased rates of both maternal problems (eg, diabetes, pregnancy-induced hypertension) and obstetrical complications (eg, preterm delivery, abnormal fetal presentation, fetal anomalies).

A solid understanding of the basic physiological mechanisms responsible for both AFV and AF composition are required to devise effective management strategies for pregnancies complicated by disorders of AFV. Current knowledge in these areas is limited, but progress is being made.

**SOURCES OF AMNIOTIC FLUID** — There are several sources for the production of AF. The relative contribution from each source changes across gestation. Knowledge of the sources of amniotic fluid can assist the investigation of patients with abnormalities of AFV. In the absence of ruptured membranes, oligohydramnios is most often a result of decreased fetal urine flow; possible causes include an obstruction of the urinary tract, as well as decreased fetal renal blood flow. Maternal dehydration with decreased placental water flow is also associated with decreased amniotic fluid. In contrast, reductions in fetal lung fluid flow are not etiologic in oligohydramnios. (See "[Oligohydramnios](#)", [section on 'Etiology'](#).)

Polyhydramnios may be associated with increased fetal urine flow due to a variety of causes, such as poorly controlled maternal diabetes resulting in fetal glycosuria, fetal heart failure due to a tachyarrhythmia or severe anemia, and many others. A reduction in fetal swallowing due to a high gastrointestinal obstruction or fetal neurologic abnormalities may be associated with severe polyhydramnios. Fetal cystic adenomatoid malformation of the lung may result in polyhydramnios, as a result of increased lung fluid secretion or esophageal obstruction. (See "[Polyhydramnios](#)", [section on 'Etiology'](#).)

**Early gestation** — There are two fluid sacs that surround the embryo during early pregnancy: the amniotic sac containing AF and the exocoelomic cavity containing coelomic fluid (ie, extraembryonic coelomic fluid). These sacs contain large amounts of liquid relative to the size of the embryo/fetus.

**Coelomic fluid** — Coelomic fluid is present between the developing chorionic and amniotic membranes beginning at about the 7th week of gestation, reaching a maximal volume around the 10th week, and subsequently decreasing in amount until it completely disappears at 12 to 14 weeks of gestation with subsequent fusion of the amniotic and chorionic membranes. The source and mechanisms that regulate the volume and composition of coelomic fluid have not been investigated directly, although the quantity and composition of this fluid have been described extensively, particularly in regard to potential biochemical markers for fetal development [4-6].

The composition of coelomic fluid is similar to maternal plasma and different from AF, suggesting that maternal plasma may be its source. However, a pathway for movement of fluid from maternal plasma to the exocoelomic cavity has not been defined. Endometrial gland secretions may be one source.

The cause of the disappearance of coelomic fluid is unknown. It is likely that solutes and fluid from the exocoelomic cavity cross the amniotic membrane into the AF and that coelomic fluid is an early source of AF.

**Amniotic fluid** — The volume of AF increases prior to the transition from embryo to fetus (ie, 10 weeks of gestation). Early pregnancy AF is likely derived from three sources:

- The fetal surface of the placenta
- Transport from the maternal compartment across the amnion (transmembranous)
- Secretions from the surface of the body of the embryo.

The relative contributions of these potential sources are unknown. However, the important late gestational sources of AF (fetal urine and lung liquid) do not contribute to the AFV in early gestation. Both coelomic and amniotic fluids are present in anembryonic pregnancies, indicating that the fetus may not be the primary fluid source in early pregnancy.

**Mid gestation** — Fetal urine begins to enter the amniotic sac and the fetus begins to swallow AF in conjunction with the transition from embryo to fetus, although the daily volume flows are quite small at mid gestation [7,8]. The fetal lungs also begin to secrete liquid into the AF at this time.

**Late gestation** — Abundant human and animal data are available regarding the source and composition of AF during the latter half of gestation. The developing human fetus becomes sufficiently large near term to allow noninvasive methods (eg, ultrasound) to estimate volumes and flows; in addition, direct measurements in chronically catheterized ovine fetuses can be conducted at this time. There appear to be two major sources for both AF production and clearance near term:

- Production — fetal urine and fetal lung liquid
- Clearance — fetal swallowing and intramembranous pathway.

The intramembranous pathway refers to water and solute exchange that occurs directly between AF and fetal blood [1,9,10]. This occurs primarily across microscopic fetal vessels present on the fetal surface of the placenta in primates and over the whole membrane surface in species with vascularized membranes. Smaller contributions may occur across the umbilical cord and fetal skin, however, transcutaneous flow ceases with skin keratinization at 22 to 24 weeks of gestation. Aquaporins (cell membrane water channel proteins) in the chorioamniotic membrane and placenta may play a role in intramembranous fluid resorption [11].

The minor sources of AF production and clearance include:

- Production — secretions from the fetal oral-nasal cavities
- Clearance — transmembranous pathway.

The transmembranous pathway refers to water and solute exchange between AF and maternal blood across the decidua and myometrium. In contrast to intramembranous flow, which occurs from one fetal compartment to another, transmembranous flow takes place between maternal and fetal compartments. Transmembranous water and solute fluxes are immeasurably small, although these exchanges were once considered major contributors to AFV and composition [1].

Both the transmembranous and intramembranous pathways permit flow of water and solutes in opposite directions (ie, osmotic flow of water and diffusion of solutes), while the other pathways only allow flow of water and solutes in the same direction (ie, bulk flow) [1].

Aside from transmembranous flow, all AFV ultimately derives from water flow across the placenta from mother to fetus.

Alterations in maternal hydration can result in changes in AFV, presumably due to changes in transplacental water flow [12,13].

Daily fetal urine excretion and fetal swallowing are the best-described processes for AF production and clearance. However, there remain major differences in the magnitude of current estimates of human fetal urine production [14-16]. We feel the best estimates of daily amniotic volume flows in the near term fetus are [17]:

- Fetal urine production — 800 to 1200 mL/day
- Fetal lung liquid secretion — 170 mL/day
- Fetal swallowing — 500 to 1000 mL/day
- Intramembranous flow — 200 to 400 mL/day
- Oral-nasal secretions — 25 mL/day
- Transmembranous flow — 10 mL/day.

These values are experimentally derived, in many cases using animal models.

**Fetal urination** — The daily volume of fetal urine excreted is approximately 30 percent of fetal body weight [1]. Hourly flow rates progressively increase from 2 to 5 mL at 22 weeks of gestation to 30 to 50 mL at 40 weeks [18,19]. The reduction in maternal plasma sodium concentration (about 5 meq/L) during pregnancy may increase the fetal urine output and contribute to AF formation by enhancing osmotic flow of water across the placenta [20]. Variations in the estimated urine flow may be

partially explained by maternal position when the measurement is obtained; maternal rest in the left lateral decubitus position markedly increases fetal urine production [21]. Another factor affecting flow rate is the time before onset of labor; hourly fetal urine production is reduced in the 14 days prior to delivery [22]. Although one report using three-dimensional ultrasonography to measure fetal bladder volume reported an hourly urine output of 125 mL at term [23], this estimate far exceeds the estimated fetal swallowed volume and intramembranous flow rates, and thus needs confirmation.

Fetal urinary flow rates decrease with conditions associated with placental insufficiency (eg, preeclampsia, fetal growth restriction) and increase with conditions associated with cardiac failure (eg, fetal anemia, supraventricular tachycardia, twin-twin transfusion syndrome). Fetal urination (and therefore AFV) is also adversely affected by obstructions in the fetal urinary tract.

**Fetal lung secretions** — The fetal lung secretes 100 times as much fluid as is needed to expand the developing lungs to facilitate their growth. The excess fluid exits the trachea, primarily during episodes of fetal breathing [24]. Approximately 50 percent of this fluid (170 mL/day) is swallowed and the remainder enters the AF compartment, which is the basis for fetal lung maturity testing [25,26]. Lung fluid secretion is reduced during periods of fetal asphyxia [1]. In addition, fetal lung fluid production ceases during labor and fluid is absorbed into the pulmonary lymphatics. In contrast, there are no known circumstances under which fetal lung fluid secretion is increased.

**Fetal swallowing** — Fetal swallowing increases throughout gestation. Although swallowing-type movements can be noted by ultrasound late in the first trimester, these movements do not become well-coordinated until the third trimester [27,28]. Direct and indirect measurements of ovine fetal swallowing suggest that the fetus swallows AF equivalent to 20 to 25 percent of body weight [1]. The volumes swallowed are significantly greater than in adults, relative to body weight [29]. Low rates of swallowing compared to fetal urination in early and mid pregnancy account for the gradual increase in AFV during this period [29]. In contrast, increased swallowing near term, and especially postterm, may contribute to the fall in AFV at the end of pregnancy.

Fetal swallowing is decreased with a consequent increase in AFV in some fetuses with neurologic abnormalities, such as anencephaly. Fetal swallowing may also be impaired by obstruction in the fetal esophagus or duodenum.

**Intramembranous flow** — Intramembranous flow is thought to be largely driven by the large osmotic gradient between fetal plasma and AF. (See 'Amniotic fluid osmolality, sodium, and chloride' below.) The normal intramembranous flow rate has been calculated only in fetal sheep [9,30]. Changes in AF osmolality were measured over time in sheep with tracheoesophageal occlusion and continuous urinary drainage [30]. This preparation eliminated all major flows into and out of the amniotic cavity, except for the intramembranous path. Half of the normal osmolality gradient between AF and fetal blood disappeared in eight hours, suggesting that 400 mL of water per day was absorbed via this route.

**Oral-nasal secretions and transmembranous flow** — These pathways account for small volumes of fluid exchange. They are difficult to measure and have not been studied [1,10].

**AMNIOTIC FLUID OSMOLALITY, SODIUM, AND CHLORIDE** — The composition of AF reflects a combination of fetal lung liquid and fetal urine, both fluids with properties different from fetal plasma. The composition of AF is distinctively different from that of all other fetal and maternal fluids.

- **Osmolality** – Fetal and maternal blood osmolalities are equivalent across gestation. Starting in the early fetal period, AF osmolality is slightly lower than that of fetal blood and decreases further as the pregnancy progresses. AF osmolality averages 260 mOsm/kg at term compared to a blood osmolality of 280 mOsm/kg. Fetal urine osmolality is usually 50 to 60 percent of AF osmolality, although the near-term fetus can alter its urine volume and osmolality in response to hormonal signals such as vasopressin [31]. Lung liquid osmolality is similar to that of fetal plasma.
- **Sodium** – The AF sodium concentration is much lower than that of fetal blood. The fetal urinary sodium concentration is low, averaging 20 to 40 percent of AF concentrations. By comparison, fetal lung liquid sodium concentration is only modestly lower than blood sodium concentration and, thus, is significantly higher than that in the AF.
- **Chloride** – Lung liquid chloride concentration is almost twice the AF chloride concentration because lung secretion is driven by the active secretion of chloride into the future airways [32]. Fetal urinary chloride concentration is very low, 10 to 20 percent of the AF chloride concentration.

Minor constituents of AF have been studied in an attempt to find biochemical markers predicting fetal condition and/or pending labor and delivery [33]. There is little consensus in these areas, except for the prediction of fetal lung maturity (AF surfactant) and open neural tube defects (AF alpha-fetoprotein).

**REGULATION OF AMNIOTIC FLUID VOLUME** — The integration of all fluid inflows and outflows determines the ultimate volume of AF. Fetal urination, lung liquid secretion, fetal swallowing, and intramembranous absorption make significant contributions to fluid movements into and out of the AF sac in late gestation.

Although many reviews have addressed the topic of AFV regulation, no study has proven if and how this occurs [1,9,10]. For AFV self-regulation to occur, there must be a feedback mechanism to detect aberrations in AFV and return volume toward normal. These issues will be addressed by first considering normal AFV turnover and then discussing possible volume regulatory mechanisms.

**Mechanisms** — The AFV does not change significantly from day to day, but the AF itself is completely replaced. In the third trimester 1000 mL of fluid flows into and out of the amniotic cavity daily so that even small changes in one of the paths of fluid migration could rapidly affect AFV [1]. Conversely, regulation of AFV must be precise to maintain normal volumes with such high flow rates. If AFV is self-regulated in the latter half of gestation, then this must occur through adjustment of one or more of the four primary AF inflows and outflows (see ['Late gestation'](#) above).

Variations in fetal homeostasis affect the volume of fetal urine production, swallowing, and lung liquid secretion. In this respect, the AFV is a passive reflector of the fetal condition. This is illustrated by the fetus with decreased renal blood flow, which leads to decreased urine production and oligohydramnios, or the anomalous fetus that cannot swallow due to gut atresia, resulting in polyhydramnios [34,35]. Maternal disease also affects fetal homeostasis, and, in turn, AFV. Maternal dehydration increases maternal osmolality, favoring transfer of water from the fetus to the mother, which, in turn, promotes transfer of water from the AF to the fetus, presumably via the intramembranous pathway [36]. Likewise, maternal hyperglycemia can lead to increased fetal urine output and polyhydramnios. These types of alterations in AFV are presumably pathologic, and these mechanisms are not likely to be involved in normal fluid homeostasis.

Variations in intramembranous flow may be an important mechanism for AFV homeostasis. The functional importance of the intramembranous absorption pathway was illustrated in a study in which surgical manipulation of fetal sheep resulted in intramembranous flow as the sole means of AF absorption [37]. AF inflow by urine production was augmented for six days with an intraamniotic infusion of Ringer's solution. During the period of Ringer's infusion, only one of six fetuses developed hydramnios as intramembranous absorption of AF increased by more than 1000 mL/day. The authors concluded that intramembranous absorption of AF increased to maintain normal AFV in response to an excessive inflow of exogenous fluid.

The mechanism whereby intramembranous absorption of water and solutes regulates AFV and maintains homeostasis was evaluated in a series of studies on ovine fetuses [26,38-42].

- In one experiment, ovine fetuses exposed to four days of hypoxia increased urine output while maintaining normal AFV [40]. Since hypoxia is a known inhibitor of fetal swallowing, the authors speculated that intramembranous absorption of AF must have increased. This hypothesis was confirmed in a subsequent study [41].
- Another study evaluated the effects of esophageal ligation on AFV and urinary flow in fetal sheep [38]. Despite the absence of fetal swallowing, polyhydramnios did not occur and AFV actually decreased by 60 percent. The authors concluded that intramembranous absorption increased to two to three times normal levels to prevent polyhydramnios. The mechanisms increasing intramembranous absorption remain in doubt. The authors suggested that fetal urine and/or lung secretions may contain factors, such as VEGF, that increase intramembranous permeability. Their subsequent experiments, however, found no effect of lung secretions on the rate of intramembranous absorption [26].
- A subsequent investigation comparing hypoxic to nonhypoxic ovine fetuses showed that hypoxia induced a two- to four-fold increase in VEGF messenger RNA expression in fetal membranes (amnion, chorion) and placenta that was associated with increased intramembranous absorption [39].
- Intravascular infusion of large volumes of saline into ovine fetuses resulted in large increases in urinary flow and intramembranous absorption, as well as a two- to four-fold increase in VEGF messenger RNA in the amnion, chorion, and placenta [42]. AFV rose only slightly. These observations suggest that intramembranous absorption and AFV homeostasis may be regulated by alterations in VEGF gene expression.
- An ovine model showed that intramembranous solute fluxes appeared to be mediated primarily by bulk flow and passive diffusion, not by passive osmosis [43,44]. The same authors have provided a mathematical model for intramembranous flow by this mechanism [45].

In a human study, orexin-A, a stimulator of fetal swallowing, was decreased in the umbilical cord blood of fetuses with idiopathic polyhydramnios [46]. This raises the possibility that AF volume regulation could be achieved by regulating fetal swallowing. This area is new and further investigation is needed.

Other studies suggest that intramembranous absorption, and therefore AFV, may be associated with changes in the expression of aquaporin water channels (AQPs) [47-49] in the placenta and fetal membranes. AQPs are a family of cell membrane water channels found ubiquitously. Thirteen AQPs are currently known; AQP 1, 3, 8, 9 and 11 have been described in the placenta and fetal membranes of humans, sheep, and mice [49-51]. In the kidney, AQPs regulate the volume and concentration of urine, and there is evidence linking AQPs in fetal membranes and placenta to AFV:

- In wild-type mice, expression of AQP 1 in the fetal membranes is negatively correlated with AFV [49], and mice lacking AQP 1 [48,52] or 8 [53] (knockout mice) demonstrate increased AFV supporting the theory that intramembranous flow occurs through, and is regulated by, these channels. Mice with oligohydramnios due to a defect in the prostaglandin F2 $\alpha$  receptor demonstrate reduced membrane AQP 8 [54], suggesting that AQP expression may be changed as a compensatory response to AFV abnormalities.

- In humans, expression of aquaporins 1, 3, 8, 9, and 11 is greater in the amnion overlying the placenta, where intramembranous flow is thought to occur, than in the reflected amnion [44]. Other human studies have largely involved patients with idiopathic abnormalities in AFV. One report found an increased expression of aquaporin 8 in the placenta and membranes of human fetuses with polyhydramnios [55]. Similarly, another group found expression of AQP 8 and 9 to be increased in the amnion and decreased in the placenta in patients with idiopathic polyhydramnios [56]. Fetuses with oligohydramnios demonstrated decreased expression of aquaporins 1 and 3 in the membranes, and increased aquaporin 3 in the placenta [57]. All of these findings have been interpreted as compensatory responses tending to correct the AFV abnormality.

The evidence indicates the potential for alteration in intramembranous flow when AFV abnormalities are present. The signal for this alteration is unknown, and it is not clear whether the AFV is actively regulated by the fetus.

**NORMAL AMNIOTIC FLUID VOLUME ACROSS GESTATION** — There are surprisingly few studies that have measured AFV across gestation, however, the available data describe a characteristic pattern of AFV change ([figure 1](#)).

- In a review of 705 normal pregnancies from 12 different studies between 1962 and 1977, AFV was observed to increase progressively from eight weeks of gestation, peak at 34 weeks (at over 800 mL), and decline thereafter [58]. The largest variability in AFV occurred in the third trimester, probably due to greater variation in fetal urination and swallowing later in pregnancy. The use of several different dye-dilution techniques and failure to subtract blood contamination from the collections of AF at the time of hysterotomy were limitations of this analysis.
- A subsequent report of 144 pregnancies performed all of the fluid evaluations using the same dye-dilution technique and a single laboratory for the calculation of the AFV [59]. AFV increased well into the third trimester of pregnancy, with the most significant increase after 30 weeks and until term.

Both of these studies found that AFV at 36 weeks of gestation was approximately 800 mL, but they differed as to whether the volume remained stable [59] or decreased [58] at term. Potential selection bias, methodologic differences, and limited numbers of patients studied beyond 36 weeks of gestation prevent a firm conclusion regarding the normal change in AFV between 36 and 40 weeks. Nevertheless, beyond 40 weeks it is likely that mean AFV decreases, with a marked reduction in postterm patients.

## SUMMARY AND RECOMMENDATIONS

- Amniotic fluid (AF) is crucial to normal fetal growth and development. (See '[Introduction](#)' above.)
- In the second half of pregnancy, AF is produced by the fetus as urine and lung liquid, and resorbed by fetal swallowing. (See '[Late gestation](#)' above.) An additional pathway for AF resorption is the intramembranous pathway: across the amnion into fetal vessels on the surface of the placenta. The rate of fluid resorption through the intramembranous pathway changes to maintain normal amniotic fluid volume (AFV) in experimental models; mechanisms for this change are speculative. (See '[Intramembranous flow](#)' above.)
- AF volume increases in human gestation until 34 to 36 weeks of gestation. Subsequently, until term, fluid volumes do not increase and may decrease. (See '[Normal amniotic fluid volume across gestation](#)' above.)
- Variations in fetal homeostasis, caused by a variety of fetal and maternal conditions, affect the volume of AF by alterations in fetal urine production, swallowing, and (possibly) lung liquid secretion. Thus, AFV is a passive reflector of the fetal condition. (See '[Regulation of amniotic fluid volume](#)' above.)

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## GRAPHICS

### Mean amniotic fluid volume across normal pregnancy



These values represent the 50<sup>th</sup> percentile. There is considerable variability around the mean. The 5<sup>th</sup>, 50<sup>th</sup>, and 95<sup>th</sup> percentiles at 33 weeks of gestation are approximately 300, 800, and 1900 mL, respectively.

Data from: Brace RA, Wolf EJ. Normal amniotic fluid volume changes throughout pregnancy. *Am J Obstet Gynecol* 1989; 161:382.

Graphic 59704 Version 6.0

## Contributor Disclosures

**Michael G Ross, MD, MPH** Nothing to disclose **Marie H Beall, MD** Nothing to disclose **Charles J Lockwood, MD, MHCM** Consultant/Advisory Boards: Celula [Aneuploidy screening (No current products or drugs in the US)]. **Vanessa A Barss, MD, FACOG** Nothing to disclose

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