Review

Maternal-fetal fluid balance and aquaporins: from molecule to physiology

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Maternal-fetal fluid balance is critical during pregnancy, and amniotic fluid is essential for fetal growth and development. The placenta plays a key role in a successful pregnancy as the interface between the mother and her fetus. Aquaporins (AQPs) form specific water channels that allow the rapid transcellular movement of water in response to osmotic/hydrostatic pressure gradients. AQPs expression in the placenta and fetal membranes may play important roles in the maternal-fetal fluid balance.

Keywords: aquaporin; placenta; fetal membranes; maternal-fetal fluid balance

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Introduction

Water is the major component of cells and tissues. Although adults contain 55%–65% water, the fetal body consists of about 70%–90% water, with a lower percentage close to term[1, 2]. Water across the plasma membrane of cells is a fundamental activity of life, and water homeostasis during fetal development is of crucial physiological importance. Fluid balance in the fetus is dependent on its mother. For example, when the mother is dehydrated, the fetal plasma osmolality increases in parallel with the maternal plasma osmolality when the placental function is normal[3]. Maternal-fetal fluid exchange at the placenta and fetal membranes and through one pathway of exchange between the fetus and amniotic fluid can occur across the skin before full keratinization. Abortion, premature birth, amniotic fluid volume abnormality, malformation and fetal growth restrictions may result when the homeostasis of the maternal-fetal fluid exchange is disrupted. Thus, maternal-fetal fluid balance is critical during pregnancy.

The molecular mechanisms of maternal-fetal fluid balance are not known. According to researchers[4–6], several mechanisms, including aquaporins, hormones, blood pressure differences, vascular endothelial growth factor (VEGF) and behavioral regulation, play important roles in maternal-fetal fluid balance. Hormonal mechanisms include the renin-angiotensin system, aldosterone and vasopressin regulation, which are involved in the alteration of fetal renal excretion, water and sodium reabsorption, and the regulation of vascular volume. In addition, elevated levels of angiotensin II in the fetus increase blood pressure and cause diuresis, which contribute to an increase in amniotic fluid volume. Blood pressure regulation also plays a role in sodium/water homeostasis. VEGF is involved in the regulation of intramembranous blood vessel proliferation, membrane transport via passive permeation and the non-passive transcytotic vesicular movement of fluid. In utero behavioral regulations, such as fetal swallowing, are early functional developments in response to dipsogens. Several aquaporins are expressed in placenta, and aquaporins play key roles in the placental mechanism.

Aquaporins (AQPs) are small (about 30 kDa) membrane proteins that are named for their ability to increase the water permeability of the lipid bilayer of plasma membranes. There are 13 known mammalian AQPs, and certain AQPs increase the permeability to small molecules, such as glycerol (AQP3, 7, 9), urea (AQP3, 7, 8, 9) and ammonia (AQP8)[7]. AQPs are distributed in different cells in various organs and play critical roles in water and other small uncharged molecules transport across cell membranes[8–14]. AQPs facilitate transepithelial fluid transport and are involved in a variety of physiological and cellular functions, such as peritoneal dialysis[15], pleural fluid transport[16], intraocular pressure and aqueous fluid production[17], corneal endothelium fluid transport[18] and amniotic fluid volume[19].

This review discusses the role of AQPs in maternal-fetal fluid balance. The location, expression and regulation of
AQP expression in the female reproductive system

All living things reproduce. The reproductive system is essential for species survival, but it is not essential to keep an individual alive. A normal reproductive system is the basis of pregnancy and is fundamental for the maternal-fetal fluid balance.

Several subtypes of AQPs have been documented in the reproductive system of both male and female humans, rats and mice[19–28]. In the female reproductive system, AQPs are strongly expressed in the ovary, oviduct, uterus, placenta, amnion and chorion during pregnancy[19–22, 25–28]. At least nine AQP isoforms (AQP1-9) are expressed in these organs (Figure 1).

The location and expression of AQPs in the female reproductive system suggest that AQPs play important roles in the production of ovum, the secretion of hormones, the regulation of the success of fertilization and early embryonic development[29–31]. Moreover, these functions of AQPs indicate an involvement in maternal-fetal fluid homeostasis.

Placenta (pregnant temporary organ)

The placenta is a remarkable organ between the mother and her fetus and plays a key role in ensuring a successful pregnancy. During its relatively short life span, the placenta undergoes rapid growth, differentiation and maturation. Nearly all materials that are exchanged between mother and fetus occur at the placenta, and all transport across the placenta must occur across the syncytial covering of the villous tree, the syncytiotrophoblast, the villous matrix and the fetal endothelium, each of which may impose its own restrictions and selectivity.

Placental transfer

The tissue that separates maternal and fetal blood in the placenta is called the placental barrier. The mature human placenta (hemochorial type) is a discoid organ with an elaborately branched fetal villous tree that is bathed directly by maternal blood. Primates, rodents and lagomorphs have placentas of the hemochorial type.

Paracellular and transcellular are the two pathways of transfer across the placenta. The paracellular pathway across the placenta is based on the observation that the placenta is permeable to inert hydrophilic solutes that do not enter cells (eg, inulin), and its existence in the hemochorial placenta is generally accepted[32]. However, the placental barrier includes a layer of continuous trophoblast syncytiotrophoblast. Therefore, the transcellular route is very important for placental transfer. The existence of transtrophoblastic channels has been demonstrated[33, 34].

In the transcellular route, molecules pass through the plasma membranes of the cells that constitute the barrier. A transcellular pathway is available for substances such as lipid-soluble molecules, very small hydrophilic molecules and membrane carriers and channels.

Water is transferred across the hemochorial placenta through both the paracellular and transcellular routes, and its transfer may be facilitated by integral membrane water channel proteins (ie, AQPs).

Amniotic fluid (AF) circulation

Because amniotic fluid volume regulation is a key part of the maternal-fetal fluid balance, it has been the focus of research. The amniotic fluid serves as a significant extracorporeal water store for fetal development, including normal anatomic and fetal lung development, and as protection from fetal trauma. A normal amniotic fluid volume is critical for normal fetal growth and symmetrical development. Insufficient (oligohydramnios) or excessive (polyhydramnios) amniotic fluid volume is associated with impaired fetal outcome, including fetal structural or functional abnormalities.

Amniotic fluid volume is dependent on gestational age, and a high regulatory ability maintains the amniotic fluid volume within a fixed range[35]. Amniotic fluid pathways include the production of fetal urine, fetal swallowing, fetal lung secretion and intramembranous and transmembranous pathways[36, 37].

A variety of factors, such as postmaturity syndrome, maternal disease, maternal medications, altitude, fetal malformations and abnormal fetal weight, may affect amniotic fluid volume[36]. Although the regulation of amniotic fluid circulation is poorly understood, the flow of water across biological membranes and the function of membrane water channels is involved.
AQP and maternal-fetal fluid balance

AQP expression in placenta and fetal membranes

Placenta varies in rodents, sheep and humans. Consistent with previous research, our studies have demonstrated that AQP1, 3, 8, and 9 are the major AQPs in the placenta and fetal membranes. This localization indicates a possible functional role in fluid homeostasis. The location of AQPs in placenta and fetal membranes is summarized in Table 1.

Table 1. AQPs location in placenta and fetal membranes of human, mouse and ovine.

| AQP   | Species      | Location                                      | References |
|-------|--------------|-----------------------------------------------|------------|
| AQP1  | Human, Mouse | vascular endothelial cell, syncytiotrophoblasts, epithelial cells of the amnion, cytotrophoblasts of the chorion | [38, 44]   |
|       | Ovine        | amnion, vessel walls of placental labyrinth    | [19]       |
| AQP3  | Human        | placenta syncytiotrophoblasts, chorion cytotrophoblasts, amnion HST cells | [39, 55, 56] |
|       | Mouse        | amnion, labyrinth trophoblast cells            | [14]       |
|       | Ovine        | cytotrophoblasts of chorion and placenta, fibroblasts of amnion and allantois | [19]       |
| AQP8  | Human        | amnion and chorion epithelial cells, trophoblasts | [28, 40]   |
| AQP9  | Human        | amnion epithelial cells, cytotrophoblasts of chorion, trophoblasts | [41, 56]   |
|       | Ovine        | epithelial cells amnion and allantois          | [57]       |

AQP expression regulation in placenta and fetal membranes

Ontogeny expression of AQPs in placenta and fetal membranes

Several AQP subtypes are expressed in placenta and fetal membranes, and an alteration in the expression of AQPs has been detected during pregnancy. Our previous study demonstrated that the ontogeny of mRNA expression for AQP1, 3 and 8 in the ovine placenta at different gestational ages (27, 45, 66, 100, and 140 d, where term is ~150 d). AQP1 was the only aquaporin present in the vasculature and was significantly higher at 27 d of gestation compared to the other time points. This result suggested that AQP1 might be related to placental angiogenesis. AQP3 was increased significantly across the gestational period, and the increase in expression coincided with a substantial increase in urea permeability in the ovine placenta.

Beall et al demonstrated that advancing gestation was associated with an increase in amniotic fluid volume from gestational days e10 to e16 with a marked decrease in amniotic fluid volume from e16 to e19. Fetal membrane AQP1, placental AQP1 and AQP9 expression were negatively correlated with amniotic fluid volume, and placental AQP3 expression was positively correlated with amniotic fluid volume.

The above results indicate that AQPs play roles in placental development and placental functions. Moreover, these results imply that the ontogeny of AQP expression is related to maternal-fetal fluid balance.

AQP expression in placenta with abnormal amniotic fluid volume

Amniotic fluid is essential for the developing fetus to provide the appropriate aquatic environment for symmetrical and normal development. Abnormal amniotic fluid volume induces premature delivery, fetal growth restriction, fetal distress, meconium aspiration syndrome, malformations and fetal death. Compared to normal amniotic fluid volume, Mann et al detected a significant increase in AQP1 expression, particularly in the amnion (33-fold) of polyhydramnios. Zhu et al also indicated that there was a significant decrease of AQP1 and AQP3 expression in the amnion and chorion of the oligohydramnios group, but AQP3 expression in placenta was significantly increased compared to the normal amniotic fluid volume group.

Our preliminary studies have shown that the expression of AQP1 mRNA is significantly lower in oligohydramnios placenta and fetal membranes than in normal pregnancy at term. The expression of AQP8 mRNA is significantly lower in oligohydramnios placenta than in normal pregnancy placenta at term. The expression of AQP9 mRNA in fetal membranes is significantly higher in polyhydramnios groups than in controls. AQP1, 3, 8, and 9 may play important roles in the maintenance of amniotic fluid volume and the balance of different components in oligohydramnios and polyhydramnios patients.

The above results indicate that the change in AQP expression in human placenta is related to amniotic fluid volume regulation. Furthermore, more evidence at the molecular level demonstrates that AQPs have an important effect on amniotic fluid volume and maternal-fetal fluid balance.

Direct evidence from AQP gene knockout mice

The AQP gene knockout mice (AQP-KO) have been studied for years and have provided direct evidence of their physiological functions. Several analysis of AQP-KO mice have revealed that AQP-knockout mice induce unexpected physiological changes, including an impairment of angiogenesis and cell migration, saliva secretion disability, cerebrospinal fluid (CSF) dynamics, peritoneal dialysis, urinary concentrating ability disturbances and polyhydramnios.

AQP1 plays an important role in angiogenesis and endothelial cell migration. In AQP1-knockout mice, aortic endothelia migration and wound healing is greatly impaired, but abnormal vessel formation is observed in vitro. The mechanism proposed is that water influx at the tip of a lamellipodium results
in membrane protrusion in the direction of cell migration\textsuperscript{[40]}. AQPs play roles in saliva secretion by transepithelial fluid transport. Osmotic equilibration is impaired in AQP5-knockout mice, which results in a reduced volume of relatively hypertonic fluid secretion\textsuperscript{[50]}. AQPI is strongly expressed at the ventricular facing surface of the choroid plexus epithelium (CPE). CSF production and intracranial pressure (ICP) are decreased in AQPI-knockout mice. Water transport by AQPI is a substantial percentage of choroidal CSF production, and a deficiency of AQPI-mediated transcellular routes may contribute to the decrease in CSF following a reduction in ICP\textsuperscript{[51]}. AQPI-knockout mice show a decreased initial and cumulative ultrafiltration (UF) without sodium sieving during peritoneal dialysis (PD). This result supports the essential three-pore theory and a similar mechanism in the descending vasa recta\textsuperscript{[52]}. AQPI is also strongly expressed in the proximal tubule of the kidney, the descending limb of Henle epithelia and in the vasa recta endothelia. Urinary concentrating ability is severely impaired in AQPI-knockout mice. The primary renal defect in AQPI knockout mice is the inability to generate a hypertonic medullary interstitium by countercurrent multiplication\textsuperscript{[53,54]}. 

Mann et al\textsuperscript{[20]} have shown that AQPI gene knockout mice have a greater amniotic fluid volume and lower amniotic fluid osmolality than wild-type and heterozygote counterparts. The result represents the movement of water through the AQPI channel because of the impaired renal fluid absorption and concentrating ability in AQPI-knockout mice. Moreover, deficiency in the regulation of water movement across the fetal membranes and within the placental trophoblast may be another mechanism for this result. AQPI in fetal membranes may contribute to amniotic fluid volume regulation, and it is speculated that idiopathic polyhydramnios may be associated with a deficiency in AQPI in human fetal membranes.

Our research in AQPI-knockout pregnant mice is consistent with the above results. For example, our study showed an increase in embryo numbers, heavier placental and fetal/ neonatal weight and an increase in the amount of amniotic fluid in AQPI-knockout pregnant mice\textsuperscript{[28]}. The results of the pregnant phenotypes of AQPI-knockout mice provide direct evidence that AQPs play important roles in pregnancy, fetal growth and maternal-fetal fluid balance. Therefore, screening for aquaporin mutations in genetic diseases associated with abnormalities in fluid balance may be required.

In summary, successful pregnancy requires high-quality ovulation, successful fertilization and normal embryonic and fetal development, in which water homeostasis plays a key role throughout pregnancy. The location, expression and regulation of AQPs in the female reproductive system, placenta and fetal membranes, coupled with direct evidence from AQPI-knockout mice support the involvement of AQPs in this physiological process and maternal-fetal fluid balance.

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