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Expression and significance of aquaporins during pregnancy

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1. ABSTRACT

Outcome of a pregnancy is dependent on high-quality ovulation, successful fertilization, normal embryonic and fetal development, and homeostasis of amniotic fluid. Throughout pregnancy, aquaporins are expressed in the placenta, uterus, adnexa, brain, urinary system, and the lacrimal gland. The regional and temporal regulation of aquaporins play important roles in normal pregnancy, fetal growth, and homeostasis of amniotic fluid volume, and water handling in other organs. The pregnant phenotypes of aquaporin-knockout mice provide direct evidence that aquaporins deficiency results in adverse outcome of pregnancy. Therefore, screening for modulation of aquaporin in abnormal pregnancy becomes desirable. Alteration of aquaporins is seen in preeclampsia, abnormal amniotic fluid volume, chorioamnionitis, and maternal under-nourished pregnancy. Although the functional importance of aquaporins remains to be elucidated, its expression and regulation in abnormal pregnancy suggests potential therapeutic strategies for the treatment of abnormal pregnancy.

2. INTRODUCTION

Aquaporins are trans-membrane proteins that organize in membrane as homotetramers. They are channels facilitating the water and small neutral solutes

across a variety of biological membranes. In mammals, there are at least thirteen aquaporins (aquaporin 0–12), which are distributed in different organs (1). Throughout pregnancy, aquaporins are expressed in the female reproductive system, placenta, fetal membranes, brain, urinary system, and lacrimal gland (2-35). To date, seven aquaporins (aquaporin 1, 3, 4, 5, 8, 9, 11) have been shown to be expressed in placenta and chorionic villi during normal pregnancy-(2-17). However, aquaporins are not only involved in several physiological processes, but also in multiple clinical dysfunctions during pregnancy.

Amniotic fluid is essential for fetal growth and development. Water absorption across the fetal chorioamniotic membranes is a critical regulatory pathway for amniotic fluid volume homeostasis. The placenta also plays a key role in a successful pregnancy as the interface between the mother and her fetus. It is well known that aquaporins increase cell plasma membrane water permeability 5-50-fold as compared with membranes in which water moves primarily through the lipid bilayer (1). Thus, aquaporins expression and alteration in the placenta and fetal membranes may play important roles in the maternal-fetal fluid balance, which contribute to amniotic fluid flux regulation and amniotic membrane tissue remodeling during pregnancy. However, the underlying molecular and cellular mechanisms remain to be elucidated. In this review, we discuss the expression, alteration and regulation of aquaporins throughout pregnancy as well as the importantance of aquaporins in amniotic fluid volume homeostasis. It will help us to understand the mechanism of abnormal pregnancy and provide potential therapeutic approaches for abnormal pregnancy.

3. EXPRESSION AND ALTERATION OF AQUAPORINS DURING NORMAL PREGNANCY

3.1. Expression and alteration of aquaporins in placenta during normal pregnancy

3.1.1. Expression/location of aquaporins in placenta in normal pregnancy

3.1.1.1. Expression/location of aquaporin 1 in placenta during normal pregnancy

Aquaporin 1 mRNA and protein were found in human amnion and chorion throughout human gestation (2) and localized in amnion epithelia and chorion cytotrophoblasts (4). Mann *et al.* (3) futher identified aquaporin 1 in the human amnion epithelium of both the chorionic plate and reflected region of the fetal membranes. In human placenta, aquaporin 1 was detected in the endothelium of placental blood vessels, but not in the placental trophoblast cells (4).

Similarly, studies in animal models (5-7) showed aquaporin 1 expression was confined to endothelial cells of the placental vasculature, but not in any epithelial cell of the placenta and fetal membranes. Kobayashi *et al.* (8) investigated the subcellular localization of aquaporin 1 in the amniotic membranes during pregnancy in mice, and found that aquaporin 1 was localized in the cell membrane of the amniotic fibroblasts but not in the amniotic epithelial cells.

3.1.1.2. Expression/location of aquaporin 3 in placenta during normal pregnancy

In the study of Mann *et al.* (3), neither aquaporin 3 mRNA nor aquaporin 3 protein expression was detected in the human amnion. Conversely, Wang *et al.* (9) and Prat *et al.* (2) detected aquaporin 3 mRNA and protein in human chorion, and amnion. Our previous study (4) and Wang *et al.* (9) further localized aquaporin 3 protein expression in placenta syncytiotrophoblasts and cytotrophoblasts, chorion cytotrophoblasts, and amnion epithelia, but no aquaporin 3 protein expression was detected in capillary endothelium or vasculature of chorion or placenta. In addition, Damiano et al. (10) found aquaporin 3 was expressed in the apical membranes of the human term placental syncytiotrophoblast.

Studies in ovine models (5) showed both the mRNA and protein of aquaporin 3 were expressed in the epithelia of the placenta and chorion and in fibroblasts within the amnion and allantois, but not within the epithelium of the amnion and allantois. On the contrary, studies in mice models (8) found aquaporin 3 was expressed in the amniotic epithelial cells during pregnancy. In addition, Aralla *et al.* (7) found aquaporin 3 was present in the placental labyrinth, amnion, allantois and yolk sac during canine pregnancy.

3.1.1.3. Expression/location of aquaporin 4 and aquaporin 5 in placenta during normal pregnancy

De Falco *et al.*(11) investigated the localization and expression of aquaporin 4 in the human placenta during gestation and found aquaporin 4 expression not only in the syncytiotiophoblast from the first to the third trimester of gestation, but also in endothelial cells and stroma of placental villi. Besides expressed in placentas from normal term pregnancies, aquaporin 4 and 5 expression was found in human chorionic villi samples from 10th to 14th week gestation (12). Aralla *et al.* (7) described a specific staining of aquaporin 5 in the amniocytes and in the columnar cells of allantochorion during canine pregnancy.

3.1.1.4. Expression/location of aquaporin 8 in placenta during normal pregnancy

Aquaporin 8 was expressed in human placenta and fetal membranes (2) with a pattern similar to those described in other species, such as canine (7) and mice (8). Wang *et al.* (13) reported the first evidence of aquaporin 8 gene expression in human amnion, chorion, and placenta. Their study clearly showed that aquaporin 8 gene was expressed in epithelia of amnion and chorion and of the syncytiotrophoblasts and outer layer trophoblasts of placenta, but lacked in the umbilical cord. After that, they (14) used reverse transcriptase–polymerase chain reaction and detected aquaporin 8 gene expression in human amnion–derived WISH cells. In addition, our previous study (15) and Qi *et al.* (16) found that aquaporin 8 protein was expressed in the cell membrane and cytoplasm of human amnion epithelial cells, chorion cytotrophoblasts

and placental trophoblasts, not in placental vascular endothelial cells.

3.1.1.5. Expression/location of aquaporin 9 in placenta during normal pregnancy

In human placenta, the expression of aquaporin 9 mRNA and protein were found in epithelial cells of amnion, chorion cytotrophoblasts, and placental syncytiotrophoblasts and cytotrophoblasts, but not in umbilical cord (3,17). Meanwhile, the study by Wang *et al.* (18) showed the expression of aquaporin 9 mRNA and protein in ovine amnion and allantois, but not in placenta, chorion, or umbilical cord. As to subcellular localization of aquaporin 9, Damiano *et al.* (10) firstly identified aquaporin 9 in apical membranes of human syncytiotrophoblast cells, whereas Aralla *et al.* (7) found aquaporin 9 was randomly expressed at the level of the basal, lateral and apical cell membrane at all the stages of canine pregnancy. During pregnancy in mice, aquaporin 9 was detectable only in the apoptotic cells of the amniotic epithelium (8).

3.1.1.6. Expression/location of aquaporin 11 in placenta during normal pregnancy

It is worth noting that the study by Escobar *et al.* (12) for the first time revealed aquaporin 11 gene expression in chorionic villi between 10th and 14th weeks of gestation. aquaporin 11 expression was established in amniotic membranes at term (2). At the same time, Prat *et al.* (2) found aquaporin 11 mRNA and proteins were present in amnion and chorion throughout human gestation and expressed in the WISH cell line.

3.1.2. Alteration of aquaporins in placenta during normal pregnancy

During normal pregnancy, the amniotic membranes gradually expand together with fetal development and the increase of amniotic fluid volume. As gestation progresses changes in amniotic fluid volume are paralleled by concomitant changes in aquaporins expression, many researchers have investigated alterations in the expression of aquaporins throughout pregnancy.

3.1.2.1. Quantitative changes of aquaporins expression during normal pregnancy

Johnston H *et al.* (5) showed that aquaporin 3 mRNA was present in the ovine placenta and chorion from at least 60 days of gestation (term is 145–150 days of gestation) with levels increasing substantially (>16 fold) at 100 days, and remaining constant thereafter. Furthermore, Liu *et al.* (6) compared the level of aquaporin 1, 3 and 8 mRNA expression in the ovine placenta at five stages of gestation (27, 45, 66, 100 and 140 days of gestation). They found that the only aquaporin present was aquaporin 1 at 27 days before significant trophoblast development had occurred, aquaporin 1 level was significantly higher at 27 days' gestation compared to other time points, because this gene was expressed only in placental vasculature (5). Aquaporin 3 was quantitatively the most highly expressed aquaporin at 66, 100, and 140 days. From 45 days' gestation, aquaporin 3 is the major aquaporin, which increases throughout gestation, and was quantitatively the most highly expressed aquaporin gene in the ovine placenta. Similarly, aquaporin 8 is also present at significant levels from 45 days' gestation, there was also a significant increase in aquaporin 8 at 100 days and 140 days' placenta compared to that at 27 days'. A substantial increase of aquaporin 3 and aquaporin 8 in the trophoblast cell coincides with the high water permeability of the placenta.

From the first to the third trimester of human gestation, De Falco *et al.* (11) observed a decrease of aquaporin 4 expression in the syncytiotrophoblast, in contrast with an increased expression in endothelial cells and stroma of placental villi, and unchanged expression in the cytotrophoblast. The aquaporin 4 expression pattern in human placenta during gestation seems to suggest aquaporin 4-mediated maternal-fetal fluid exchange could play a key role in the control of ion homeostasis and water balance in the human placenta throughout pregnancy.

Escobar *et al.* (12) compared aquaporins expression in human chorionic villi samples between 10th and 14th weeks of gestation with that in placentas from normal term pregnancies (38-40 weeks gestation) and identified high mRNA expression for aquaporin 1, 3, 9 and 11, low for aquaporin 4, 5, and 8, and non-detectable for aquaporin 2, 6, and 7 in chorionic villi. Furthermore, they found chromosomal abnormalities did not alter aquaporins' expression.

3.1.2.2. Alteration of cellular localization of aquaporins

Cellular and subcellular localization of aquaporins in amniotic membranes during pregnancy have been observed in mice (embryonic day 10, 12, 14, 16 and 17) (8). On embryonic day 10 (E10), aquaporin 1 was not detected in the amniotic membrane. From E12 to E14, aquaporin 1 was increased in the amniotic fibroblasts. On E16, aquaporin 1 was present in the plasma membrane. On E17, aquaporin 1 was observed in the cytoplasm around the nucleus, in addition to the plasma membrane.

Between E10 and E12, aquaporin 3 was present in both epithelial cells and fibroblasts. Then, its distribution in the epithelial cells dynamically changed as follows: at E14 in the lateral membrane and apical junction; at E16 in the lateral membrane alone; at E17 in the lateral membrane and cytoplasm.

On the other hand, aquaporin 8 was expressed in the epithelial cells and complementarily localized in the apical junction and the lateral membrane. Aquaporin 9 was not identified in the amniotic membrane until E16. On E16 and E17, Aquaporin 9 was detected only in the apoptotic cells of the epithelium. These cellular and subcellular localizations of amniotic aquaporins indicate that each aquaporin plays distinct functional roles, such as in water and urea transport, cell migration, cell proliferation and apoptosis, and amniotic fluid homeostasis or tissue remodeling of amniotic membranes.

3.1.2.3. Differences between mRNA and protein expression patterns of aquaporins

Aquaporins mRNA and protein expression patterns in fetal membranes were not identical during human pregnancy (2). Aquaporin 1 presented the highest

levels of expression during the first trimester and globally tended to decrease after 11 weeks of gestation (WG). Indeed, both 11 and 21 WG marked significant increases in aquaporin 1 mRNA quantity in terms of total membranes, and amnion and chorion taken in isolation followed a similar pattern. Protein expression also peaked at 11 WG, with a second peak at 26 WG instead of at 21 WG.

Aquaporin 3 mRNA is principally present at 12 WG and at 26 WG in healthy human fetal membranes, whereas the protein pattern of aquaporin 3 showed a single peak at 18 WG. Despite these differences between mRNA and protein expression patterns, the results globally showed a sharp increase in aquaporin 3 from 12 to 26 WG (i.e., spanning the first and second trimesters) and weak aquaporin 3 expression during the third trimester of pregnancy.

In addition, high aquaporin 8 mRNA expression was detected as early as 10 WG, and aquaporin 8 protein expression peaked at 11 and 12 WG. A second high peak of aquaporin 8 was detected at 18 WG at transcript level but not at protein level. Aquaporin 9 protein expression levels showed no significant pattern change during gestation, whereas aquaporin 9 mRNA expression peaked at 21 WG. The 18-21 WG period marked the highest level of aquaporin 11 mRNA expression, while aquaporin 11 protein showed an accumulation at term.

These results indicate that each aquaporin has a time-specific expression pattern, and aquaporins are expressed and potentially involved in the regulation of amniotic fluid homeostasis throughout pregnancy.

3.2. Expression and alteration of aquaporins in uterine during normal pregnancy

Some researchers have found that expression of aquaporins in uterine play an important role in water handling during implantation, early pregnancy and parturition. In consistent with their function, the expression and distribution of some aquaporins are altered in uterine.

3.2.1. Expression and alteration of aquaporins in corpus during normal pregnancy

Richard *et al.* (19) examined the expression of aquaporins 0-9 in the mouse uterus on day 1-8 of pregnancy and showed distinct uterine expression patterns for aquaporin 1, 4, and 5. Aquaporin 1 was localized to the inner circular myometrium throughout the periimplantation period. Aquaporin 4 was highly expressed in the luminal epithelium on day 1 of pregnancy but barely detectable at the time of implantation. Aquaporin 5 was expressed at low levels in the glandular epithelium during early pregnancy but was markedly increased on day 5. They also observed expression of aquaporin 8 in the inner-cell mass and aquaporin 9 in the mural trophectoderm of the implanting blastocyst. Collectively, these results suggest that members of the aquaporin family are involved in embryo and uterine fluid homeostasis during implantation.

Lindsay *et al.* (20) revealed the absence of aquaporin 4 in the rat uterus during early pregnancy. Immunofluorescent and immunogold techniques showed that there was a shift of aquaporin 5 to the apical surface of uterine epithelial cells in the mesometrial pole of the uterus at the time of implantation. Detailedly, on days 1 and 3 of pregnancy, there was only faint staining of aquaporin 5 in uterine epithelial cells. By day 6 of pregnancy, aquaporin 5 staining was more intense at the apical surface of uterine epithelial cells and was strongest at the mesometrial pole of the uterine lumen which continued on day 7 of pregnancy. Little or no immunofluorescence was present in the antimesometrial uterine epithelium. By day 9 of pregnancy, aquaporin 5 was still localized apically but the intensity was similar throughout the uterus. These results suggest that aquaporin 5 plays an important role in the removal of uterine luminal fluid at the time of implantation in the rat and may contribute to the antimesometrial positioning of the implanting blastocyst.

Aquaporin 1 was localized in stromal blood vessels (20) and to the plasma membrane of smooth muscle cells found within the inner circular layer (21) in the rat uterus. There was no change in uterine epithelial cells during early pregnancy. However, the intensity of aquaporin 1 immunoreactivity increased in the rat myometrium. In particular, an increase was also observed in mesometrial as compared to antimesometrial myometrium. It is suggested that aquaporin 1 plays a role in stromal edema, uterine closure and orientation of the blastocyst at the time of implantation.

A functional and distinctive collaboration exists among diverse aquaporins in water handling within the pig uterus during the different uterine phases in the estrous cycle and early pregnancy. Skowronski (22) demonstrated that aquaporin 1, 5, and 9 were clearly detected in all studied stages. Expression of aquaporin 1 within uterine endometrial and myometrial blood vessels and myometrial expression of aquaporin 5 did not change significantly during the estrous cycle but increased during gestation. In addition, endometrial expression of aquaporin 5 and aquaporin 9 did not change significantly at the early- and middle-luteal phase of the estrous cycle but increased at the late-luteal phase and the follicular phase of the estrous cycle as well as during early pregnancy.

As a potential role for glycerol transport, aquaporin 7 is dynamically expressed in mouse uteri undergoing decidualization after implantation (23). Immediately after the initiation of embryo attachment, aquaporin 7 showed a specific increase around the attachment site of embryo implantation. This expression pattern further expanded with the decidualization process in the uteri of day 6–8 of pregnancy, which was associated with elevated uterine glycerol accumulation and glycerol kinase expression, suggesting that aquaporin 7 as a general glycerol gateway was involved with energy metabolism of uterine in postimplantation.

Using high-density DNA microarray, Helguera G *et al.* (24) detected the changes in global gene expression in rat myometrium in transition from late pregnancy to parturition. They found aquaporin 5 was dramatically

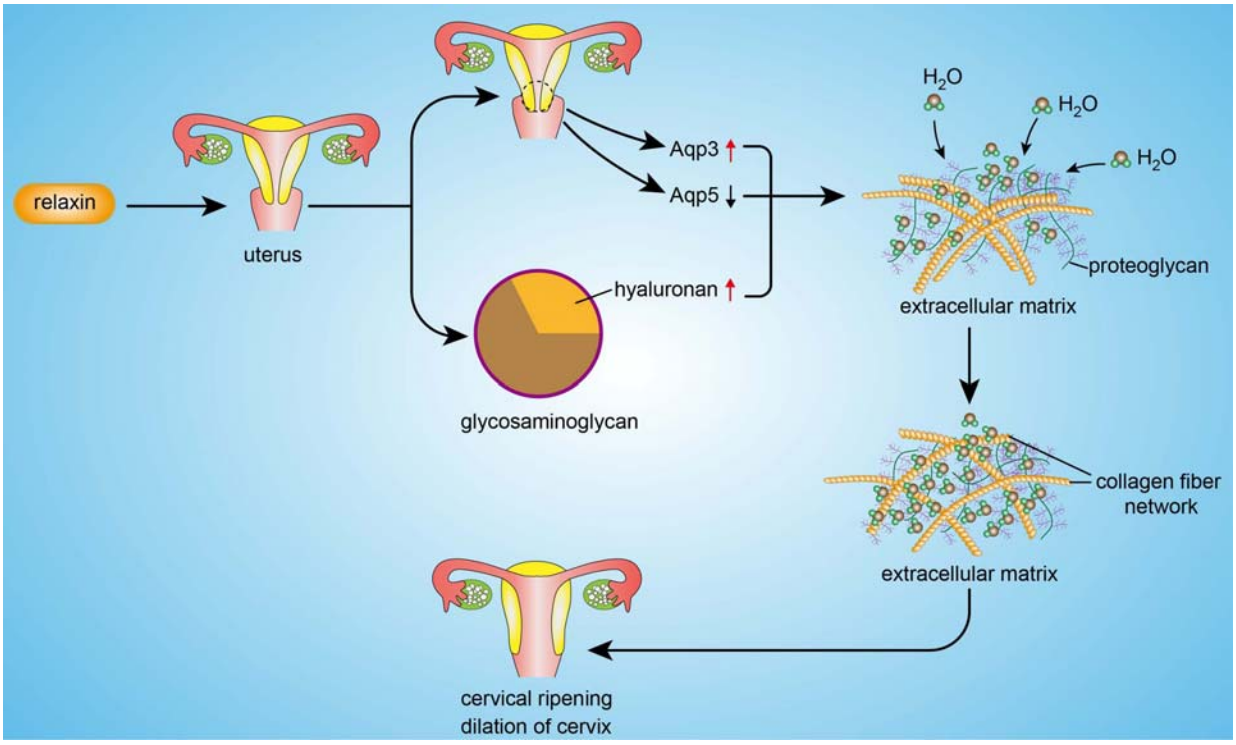

Figure 1. Relaxin regulates cervical ripening via aquaporin 3 and 5. Relaxin regulated aquaporin 3 and 5 expression in the cervix and initiated changes in glycosaminoglycan composition through increased hyaluronan synthesis. These actions of relaxin collectively promote water recruitment into the extracellular matrix to loosen the dense collagen fiber network, which was associated with cervical ripening, thus enabling the cervix to dilate at term.

downregulated during parturition, approximately 100-fold by microarray and approximately 50-fold by real-time PCR, undercovering its potential role in parturition.

3.2.2. Expression and alteration of aquaporins in cervix during normal pregnancy

Of the 13 known murine aquaporins, aquaporin 0-2, 6, 7, 9, 11, and 12 were absent or at the limits of detection in the mouse cervix during parturition. By in situ hybridization and immunohistochemistry, aquaporin 3 was preferentially expressed in basal cell layers of the cervical epithelium, whereas aquaporin 4, 5, and 8 were primarily expressed in apical cell layers (25). Aquaporin 3 expression was low in nongravid and mid-pregnancy cervices with peak expression on day 19 and postpartum day 1. Aquaporin 4 expression was generally low throughout pregnancy but showed a small upward trend at the time of parturition. Aquaporin 5 and 8 expression were significantly increased on day 12-15 but fell to nongravid/baseline by day 19 and postpartum day 1. Taken together, these studies suggest that aquaporin 3, 4, 5, and 8 are involved in fluid homeostasis in the pregnant and peri-partum cervix and facilitate distinct aspects of water transport across the cervical epithelium.

Relaxin regulated aquaporin 3 and 5 expression in the cervix and initiated changes in glycosaminoglycan composition through increased hyaluronan synthesis (26). These actions of relaxin collectively promote water recruitment into the extracellular matrix to loosen the dense collagen fiber network, which was associated with cervical ripening, thus enabling the cervix to dilate at term (Figure 1).

3.3. Expression and alteration of aquaporins in adnexa during normal pregnancy

In adnexa of the female pig, aquaporin 1 was detected in the capillary endothelium of the ovary and oviduct. Aquaporin 5 was expressed in flattened follicle cells of primordial follicles, granulosa cells of developing ovarian follicles, muscle cells and epithelial cells of the oviduct. Aquaporin 9 immunoreactivity was observed in granulosa cells of developing follicles and the luminal epithelial cells of the oviduct (27).

Moreover, aquaporin 1, 5, and 9 were clearly detected within the pig oviduct during different stages of the estrous cycle and early pregnancy (28). In cyclic gilts, the expression of aquaporin 1, 5 and 9 protein did not change significantly between mid- and late-luteal phases but increased at early-luteal phase and late- follicular phase of the estrous cycle. In pregnant gilts, expression of aquaporin 1, 5, and 9 did not change significantly in comparison with the estrous cycle. These results suggested alterations of aquaporin 1, 5 and 9 within the pig oviduct might be implicated in ovum transport toward the uterus. The variation of aquaporin 1 in the endothelial cells of the vascular and lymphatic endothelium of porcine peri-ovarian

vascular complex during the estrous cycle and early pregnancy was similar to that in the oviduct (29). It may contribute to creating an environment in reproductive organs that enables formation of the ovarian follicular antrum and follicular fluid.

3.4. Expression and alteration of aquaporins in brain during normal pregnancy

To date, only three aquaporins, aquaporin 1, 4, and 9, have been shown to be expressed in brain in vivo. Pregnancy and the postpartum state up-regulated aquaporin 4 protein localized primarily around the brain parenchymal blood vessels from Sprague-Dawley rats, a consequence that could promote edema formation when blood pressure is acutely and excessively elevated, as during eclampsia (30). Wiegman *et al.* (31) assessed regional expression of aquaporins in the brain during pregnancy and showed that aquaporin 1, 4, and 9 were expressed in the anterior and posterior cerebrum, cerebellum, and brainstem of non-pregnant, mid-pregnant, late-pregnant and postpartum rats. The regional distribution pattern of aquaporin 4 and 9 remained similar during gestation, whereas this pattern changed for aquaporin 1. The expression levels of aquaporin 1, 4, and 9 in the brainstem did not change with gestation, whereas changes were found in the anterior cerebrum for aquaporin 4 and in the posterior cerebrum and cerebellum for all aquaporins.

3.5. Expression and alteration of aquaporins in urinary system during normal pregnancy

After comparing the aquaporin 2 expression between nonpregnant and pregnant Sprague-Dawley rats in renal inner medulla (papilla), Ohara *et al*. (32) demonstrated the upregulation of both the aquaporin 2 mRNA and protein in pregnancy through a V2 receptor-mediated effect. This effect occured early in gestation (day 7) and persisted throughout pregnancy, which might contribute to the water retention in pregnancy.

However, in the study by Joyner *et al*. (33), pregnancy did not alter aquaporin 1 or aquaporin 2 protein expression in whole kidney homogenate despite increased circulating arginine vasopressin. This study was differ in regard to the previous study (32), since Joyner *et al*. (33) evaluated whole kidney homogenates and not a specific medullary region. Until regional specific evaluation of aquaporin 1 in proximal tubules and descending thin limb and aquaporin 2 in collecting ducts is done during pregnancy, their role cannot be eliminated.

Urinary aquaporin 2 increased during weeks 12, 24 and 36 of pregnancy in healthy pregnant primiparas with single fetus, with the highest peaks at the 36(th) week (34). In the postpartum period, the value markedly decreased. No statistically significant changes were found in plasma arginine vasopressin levels throughout the study period. These findings suggest that a non- arginine vasopressin factor present in pregnancy plays a role in the control of the excretion of aquaporin 2.

3.6. Expression and alteration of aquaporins in the lacrimal gland during normal pregnancy

The expression of aquaporin 4 and 5 are altered in the lacrimal gland from term pregnant rabbits. These changes may contribute to the altered lacrimal gland secretion and dry eye symptoms during pregnancy (35). In term pregnant rabbits, aquaporin 5 mRNA and protein from whole lacrimal gland was significantly lower than that of normal control adult female rabbits, while aquaporin 4 protein was more abundant and aquaporin 4 mRNA was not different. Aquaporin 4 was preferentially located in ducts while aquaporin 5 in acini from lacrimal gland of pregnant rabbits, suggests that they play different roles in acinar and ductal cells. Their significant changes during pregnancy also suggest their potential site-specific involvement in pregnancy-related lacrimal gland deficiency.

4. AQUAPORIN AND HOMEOSTASIS OF AMNIOTIC FLUID VOLUME

Amniotic fluid is an essential accompaniment of pregnancy that provides the fetus a fluid-filled compartment for normal growth, movement, and development. Excess or deficient amniotic fluid volume is associated with significant perinatal morbidity. Amniotic fluid is created by the flow of fluid from the fetal lung and bladder and reabsorbed in part by fetal swallowing and partly by the transfer across the amnion to the fetal circulation (7, 36-37). The circulation of water between mother and fetus, and within the fetal compartment, is complex, and the mechanisms regulating water flow remain poorly understood. Many studies suggest that aquaporins may contribute to amniotic fluid regulation in placenta and fetal membranes.

Studies in mice models by Beal *et al.* (37) demonstrated amniotic fluid volume was negatively correlated with fetal membrane aquaporin 1 and placental aquaporin 1 and aquaporin 9 expression, and positively correlated with placental aquaporin 3 expression. Changes in aquaporins with advancing gestation, and their correlation with amniotic fluid volume, suggest a role in mediating placental and membrane water flow and ultimately amniotic fluid volume. Aquaporin 1 appears to regulate fetal membrane water flow, and aquaporin 3 is a likely candidate for the regulation of placental water flow.

In addition, studies in canine models by Aralla *et al.* (7) detected that distinct aquaporin 1, 3, 5, 8 and 9 expression patterns in fetal membranes and placenta were related to pregnancy period, in which amniotic fluid volume and biochemical composition changed. There was a collaboration of different aquaporins in the specific functions of each anatomical structure, which might contribute to the regulation of the intramembranous water flow on the basis of amniotic fluid changes.

5. REGULATION OF AQUAPORINS IN NORMAL PREGNANCY

Aquaporins regulate water flux dependent upon cellular location and cellular milieu. Many endocrine

signals may alter intramembranous flow via regulation of membrane aquaporins.

Lindsay *et al*. (38), for the first time, showed that the up-regulation of aquaporin 5 in the apical plasma membrane of uterine epithelial cells and aquaporin 1 in the inner circular layer of myometrium was dependent on progesterone, which was similar to that seen at the time of implantation. Treatment of adult ovariectomized mice with replacement steroids demonstrated an estrogen-induced shift in aquaporin 1 signals from the myometrium to the uterine stromal vasculature, suggesting a role in uterine fluid imbibition (19). In contrast, aquaporin 5 was induced only in estrogen-treated, progesterone-primed uteri.

In a series of studies done in Ross's lab, aquaporin 1, 3, 8 and 9 gene expression in human amnion epithelia were up-regulated by second messenger cyclic adenosine monophosphate (cAMP) (9, 14, 39). In human amnion–derived WISH cells, incubation with either monobutyryl cyclic adenosine monophosphate or the cyclic adenosine monophosphate-elevating agent forskolin resulted in a significant increase in aquaporin 8 mRNA level (14). In primary human amnion epithelial cell culture, which were prepared from amnion of normal-term pregnancy, aquaporin 1, 3, 8 and 9 mRNA expression increased significantly following forskolin, an adenylate cyclase activator that stimulates cellular production of cAMP, treatment. In contrast to forskolin, SP-cAMP, a cAMP agonist that stimulates protein kinase A, incubation resulted in no change in aquaporin 1, 8 and 9 mRNA expression (9, 39). Lack of effect of SP-cAMP on aquaporin 1, 8, and 9 mRNA expression suggests that cAMP upregulates human amnion aquaporin 1, 8, and 9 mRNA expression via the protein kinase A independent pathway (39). However, human amnion aquaporin 3 mRNA significantly increased at 2 hours following incubation with SP-cAMP (9).

In another reseach investigated by Ross's lab (40), arginine vasopressin significantly increased the expression of aquaporin 1 mRNA in first trimester-derived extravillous cytotrophoblasts (HTR-8/Svneo) cells. Both SP-cAMP and forskolin significantly increased aquaporin 1 mRNA expression in trophoblast cells after 2 hours in a dose-dependent manner with a parallel increase in protein expression. These results indicated that in trophoblast cells aquaporin 1 gene expression was upregulated by both arginine vasopressin and cAMP agonists. Furthermore, their data demonstrated that a cAMP-dependent pathway is responsible for the arginine vasopressin effect on aquaporin 1. Thus, modulation of aquaporin 1 expression by maternal hormones may regulate invasion and fetal-placental-amnion water homeostasis during gestation.

Interesting, Qi *et al*. (16) found that expression of aquaporin 8 in amnion epithelial cells was diversely regulated by osmotic stress. Compared to isosmolar media, hypotonic media significantly enhanced aquaporin 8 mRNA and protein expression, while hypertonic media significantly decreased expression.

6. AQUAPORIN DEFICIENCY AND PREGNANCY OUTCOME

Findings reported in some studies suggest that aquaporins deficiency plays an important role in pregnancy outcome. Mann *et al* (41) reported that aquaporin 1-knockout pregnant mice had a greater volume of amniotic fluid and lower amniotic fluid osmolality than their wild-type and heterozygote counterparts. But there were no significant differences in fetal or placental weights among the groups. The author speculate that transgenic aquaporin 1 knockout mice may provide a unique animal of polyhydramnios.

Sun *et al* (42) revealed that aquaporin 4 deficiency induced subfertility in female mice because aquaporin 4 (-/-) mice displayed a lower rate of pregnancy and decreased litter size when compared with aquaporin 4 (+/+) mice. Further studies revealed that in aquaporin 4-null mice, there were fewer numbers of antral follicles and corpora lutea in the ovaries and that uteri presented as hyporeactive to gonadotropins.

However, Su *et al* (43) identified increased female fertility in aquaporin 8 deficient mice. They found significantly increased number of offspring delivered by aquaporin 8(-/-) mothers compared with wild-type mothers in cross-mating experiments. Aquaporin 8 deficiency increased the number of mature follicles by reducing the apoptosis of granulosa cells, thus increasing the fertility of female mice. This discovery may offer new insight of improving female fertility by reducing granulosa cell apoptosis through aquaporin 8 inhibition.

In addition, comparison of the pregnant phenotype of aquaporin 8-deficient mice with that of wild type controls revealed a significantly higher number of embryos, greater fetal/neonatal weight, greater amount of amniotic fluid, larger placental weight in aquaporin 8-knockout mice (44). While there was no evidence of placental pathology in either group.

7. EXPRESSION AND REGULATION OF AQUAPORINS IN ABNORMAL PREGNANCY

7.1. Aquaporins in pregnancy with hypertensive disorder complicating pregnancy

To date, the etiology of preeclampsia has not been established. Previous studies by many researchers have found alteration of aquaporins expression in placenta play an important role in the pathogenesis of preeclampsia. Studies in rat models by Abreu *et al.* (45) showed that aquaporin 2 mRNA expression was higher in pregnancy group and in hypertension group than in non-pregnant normal control group, but it was lower in hypertension pregnancy group than in either pregnancy or hypertension group. They also found up-regulated aquaporin 2 mRNA expression contributed to water and salt retention.

Quick *et al.* (30) found that pregnancy and the postpartum state up-regulate aquaporin 4 protein located

around the intraparenchymal blood vessels, a consequence that could promote edema formation when blood pressure is acutely and excessively elevated, as during eclampsia.

Damiano *et al.* (48) demonstrated the localization of aquaporin 9 not only in apical and basal membranes but also in the cytoplasmic region in human preeclamptic placenta. They described the abundance of aquaporin 9 protein increasing by 2.5-fold in preeclamptic placentas when compared with normal term placentas. There was a lack of functionality of aquaporin 9 for water and mannitol transport, but an evidence that aquaporin 9 involved in the urea excretion mechanism across syncytiotrophoblast of human placenta from mother to fetus.

Studies by Ghabriel *et al.* (46) showed that magnesium sulphate decreased brain edema formation after traumatic brain injury, possibly by restoring the polarized state of astrocytes and by down-regulation of aquaporin 4 channels in astrocytes. However, Euser *et al.* (47) found magnesium sulphate treatment had no effect on brain aquaporin 4 protein expression after using an in vivo model of hypertensive encephalopathy in late-pregnant rats.

Many factors have been showed to regulate aquaporin 9 functionality in preeclamptic placentas. Damiano *et al.* (49) found the cystic fibrosis transmembrane conductance regulator expression was decreased in preeclampsia and may thus be implicated in the regulation of aquaporin 9 activity. Although, in preeclamptic placentas high levels of human chorionic gonadotropin could up-regulate aquaporin 9 protein expression via cAMP pathways, aquaporin 9 functionality was reduced possibly by other factors (50). In addition, authors (51) further studied whether aquaporin 9 expression in preeclamptic placenta was modulated by insulin because the aquaporin 9 gene contains a negative insulin response element. They found insulin decreased the molecular expression of aquaporin 9 exclusively in explants from normal placentas in a concentration-dependent manner, which provided new evidence that in preeclamptic placentas the mechanisms of insulin signaling may be altered, producing an overexpression of aquaporin 9 that does not correlate with an increase in its functionality.

7.2. Aquaporins in pregnancy with oligohydramnios

Oligohydramnios is diagnosed as an amniotic fluid index examined by ultrasound of 5 cm or lower according to the criterion of Phelan *et al*. (52). Most oligohydramnios cases occur at term without associated risk factors, namely isolated oligohydramnios (53). Reduction in amniotic fluid volume is associated with increased perinatal morbidity and mortality. However, the mechanism that produces oligohydramnios is still not clearly understood.

Using prostaglandin F2α receptor-deficient mice, Shioji *et al* (54) set up an oligohydramnios model and demonstrated that the aquaporin 8 expression in fetal membranes was significantly decreased at post term when oligohydramnios occurs. In our previous study, we found (4) that aquaporin 1 expression in human amnion in isolated oligohydramnios group was decreased in comparison to normal amniotic fluid volume group, but there was no significant difference in chorion and placenta between the two groups. Aquaporin 3 expression in amnion and chorion in isolated oligohydramnios group was significantly decreased, while expression in placenta was significantly increased. In addition, compared with the normal amniotic fluid volume group, the expression levels of aquaporin 8 in amnion and aquaporin 9 expression in amnion and chorion in isolated oligohydramnios group were significantly decreased, while their expressions in placenta were significantly increased (55). These findings suggest that aquaporin 1, 3, 8, and 9 may play an important role in water flow both in intramembranous absorption and in placental water transfer, which provides a potential therapeutic approach for oligohydramnios.

7.3. Aquaporins in pregnancy with polyhydramnios

Historically, approximately 50%□60% of polyhydramnios were considered idiopathic, the exact etiology being unknown. An association between idiopathic polyhydramnios and the risk of adverse pregnancy outcomes and significant perinatal morbidity has been recognized for many years (56), however, the basic pathophysiological mechanisms responsible for idiopathic polyhydramnios remain poorly understood.

There are some studies that explore the relationship between the expression of aquaporins in human placenta and idiopathic polyhydramnios. Relative to pregnancies with normal amniotic fluid volume, there was an increasing expression of aquaporin 1 in all regions of the fetal membranes, and the greatest increase (33-fold) was seen in the reflected amnion of pregnancies with idiopathic polyhydramnios (57). Compared to normal amniotic fluid volume group, the expression of aquaporin 8 in amnion, and aquaporin 9 in amnion and chorion, were significantly increased in idiopathic polyhydramnios group; however, their expression in the placenta was significantly decreased (15). These results suggest that alterations in aquaporins expression may be a compensatory response to and not a cause of idiopathic polyhydramnios.

7.4. Aquaporins in pregnancy with chorioamnionitis

Recently, the potential role of aquaporins in histologic chorioamnionitis in human pregnancy has been found. Mittal P, *et al.* (58) determined the expression of aquaporin 9 in the chorioamniotic membranes from women with and without term labor, as well as those with preterm prelabor rupture of membranes with and without histologic chorioamnionitis. The results showed that aquaporin 9 expression in fetal membranes was significantly higher in spontaneous term labor when compared with term not in labor. Among patients with preterm prelabor rupture of membranes, the presence of histologic chorioamnionitis was associated with a higher expression of aquaporin 9 in the chorioamniotic membranes compared with those from women without histologic chorioamnionitis. The study implicates a novel role for aquaporin 9 in membrane-mediated transfer of nutrients to support the increased metabolic demands associated with the host immune

response of the terminal pathway of parturition and histologic chorioamnionitis.

7.5. Aquaporins in maternal undernourished pregnancy

Belkacemi *et al*. (59) quantified protein expression of aquaporins in placenta with maternal undernutrition during pregnancy. Placental basal zone (hormone production) of pregnant rats showed variable changes in aquaporin expression unrelated to the gestational age or severity of the fetal/placental growth restriction. But in the labyrinth zone (feto-maternal exchange), maternal undernutrition placental aquaporin 1 expression was significantly decreased, whereas aquaporin 8 and 9 expression were significantly increased at days 16 and 20 of gestation. Dysregulation of aquaporins' expression prior to the occurrence of oligohydramnios may represent a compensatory mechanism under conditions of early maternal undernutrition. Arrighi *et al*. (60) demonstrated that Undernutrition during fetal to prepubertal life affected aquaporin 9 but not aquaporins 1 and 2 expression in the male genital tract of adult rats.

7.6. Aquaporins in pregnancy with intrahepatic cholestasis

Li *et al*. (61) investigated the alteration on the expression levels of aquaporin 8 mRNA and protein in the hepatocytes of pregnant rats with intrahepatic cholestasis induced by ethinylestradiol. After making the model of intrahepatic cholestasis of pregnant rats successfully, they found aquaporin 8 mRNA level in intrahepatic cholestasis group was significantly higher than in control group, while aquaporin 8 protein level in intrahepatic cholestasis group was significantly decreased. The reasons lead the disaccord between aquaporin 8 mRNA level and aquaporin 8 protein level and the role of aquaporin 8 in the pathogenesis of intrahepatic cholestasis need futher study.

8. CONCLUSIONS

In summary, aquaporins are cell membrane proteins that significantly enhance membrane permeability to water by acting as water channels. Throughout pregnancy, aquaporins are not only involved in several physiological processes but also in multiple clinical dysfunctions. Along with gestation progresses and amniotic fluid volume changes, the expression and location of aquaporins changes according to the needs of the organism. Alteration of aquaporins expression in placenta play an important role in the pathogenesis of abnormal pregnancy. Futher studys need to explore the factors regulate the expression of aquaporins in placenta, which help us to understand the mechanism of abnormal pregnancy and provide potential therapeutic approaches for abnormal pregnancy via modulation of aquaporins.

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