The dynamic placenta: II. Hypothetical model of a fetus driven transplacental water balance mechanism producing low apparent permeability in a highly permeable placenta

N.J. Sebirea,*, D. Talbertb

a Department of Histopathology, Camelia Botnar Laboratories, Great Ormond Street Hospital, Great Ormond Street, London WC1N 3JH, UK
b Institute of Reproduction and Developmental Biology, ICSM, Hammersmith Hospital, Du Cane Road, London, UK

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Summary In vitro and isotopic studies in vivo have reported the paradox that the human placenta is highly permeable, water exchanging at 3.6 litres per hour at 35 weeks of gestation, but clinical measurements in vivo show net transfer is minimal, around 2 ml/day. Current theories are based on osmotic pressure balances, but changes in maternofetal hydrostatic pressure change much faster than osmotic factors could respond. An alternative explanation might be that net transfer is not in fact the result of passive mechanisms, but is actively controlled by the fetus itself. The fetus is well equipped to monitor changes in blood volume, such as via sensors in venous and atrial stretch receptors to control ANF and hence urine production. Transplacental water regulation requires modification of transvillus pressures. Placental sub-chorial arteries and veins (of extra-embryonic origin) have different sensitivities from fetal body tissues to some vasoactive substances, and stem villous veins have unusually well developed vascular smooth muscle. It is thus theoretically possible for the fetus to modify subchorial venous resistances, and hence villous capillary pressure with a suitable circulating placental venous constrictive agent. A computer modelling study was undertaken using a fictitious placental venous constricting agent "fictensin", considered to be released by the fetus in proportion to disturbance of vascular volume. The effective placental permeability fell in proportion to the tightness of this fetal control mechanism, suggesting that the apparent placental permeability measured in vivo is a measure of fetal control, not true permeability. However, the range of compensatory pressures that the fetus can produce by this means is limited and failure of such a mechanism could allow flooding or dehydration of the feto-placental unit. This may shed new light on disorders such as polyhydramnios and fetal hydrops.

Introduction

Placental permeability to water measured in vitro appears very high and matches the rate of water exchange measured in vivo by isotope techniques.
yet in water loading experiments in vivo the permeability appears 10,000 or more times less [2]. The haemochorial human placenta allows diffusion of relatively large molecules (up to 5000 Da; [3]), through pores up to 3.6 nm effective diameter [4]. This is consistent with the high (3.6 litres per hour at 35 weeks) turnover observed in vivo by using Deuterium water injection [5], although a 3 kg fetus only requires around 20 ml/day for growth [6]. At 30 weeks of gestation it was estimated that that 3800 times as much water is exchanged between mother and fetus than is retained by the fetus for growth. This seems to rule out water transport regulation by an unrecognised osmotic, or colloid osmotic mechanism at the exchange surface itself as has been suggested for the choriendothelial sheep placenta because sodium, or any other ion would have to be moved in enormous quantities and at great energy expenditure to make any impression on these high water fluxes.

Acute changes in intervillus hydrostatic pressure occur with alterations in uterine blood flow. The fetus has been observed to respond to the onset of maternal stress [7] secondary to changes in utero-placental blood flow [8]. The placenta will also be vulnerable to changes in maternal abdominal pressure when the mother is lying supine or prone, sitting relaxed or walking fast, etc. Moreover, the hydro-osmotic pressure balance driving water through the villous surface varies across the placenta, even within cotyledons [9]. Pressure in the core region, subject to the force of the spiral artery outlet jet is higher than that between cotyledons, indeed it has to be, to effectively drive maternal blood through the intervillus space. This pressure gradient also drives water into villi in each core region and allows water to leave at the cotyledonary periphery in an analogous manner to the movement of water out of any somatic capillary at its arteriolar end and back inwards at its venular end [10]. Such pressure gradients also depend both on the individual spiral artery flows and the corresponding cotyledons intervillus flow resistance. During pregnancy both will change particularly the latter, with villus proliferation, fibrin deposition, etc. [11]. All the individual water transfers in each cotyledon need to be integrated to find the net water movement. If the placenta itself were to balance these local factors it would need some form of neural network to perform the integration and this manifestly is not present.

On the contrary, the fetus can monitor its blood volume and adjusts urine output to maintain optimum water balance. Furthermore, both villus stem arteries and veins have well developed vascular smooth muscle (Fig. 1). In arteries this probably provides myogenic pressure regulation [12]. The possibility that myogenic stem arteries could auto-regulate mean capillary pressure was investigated, but no effective configuration was found. Such vascular smooth muscle development in veins having no innervation is more difficult to explain in a passive placenta, but if it were part of a fetal compensatory mechanism, the thicker muscle would allow water transfer control over a wider range of pressures. Constriction in these stem veins would raise intra-villus hydrostatic pressure driving water to the mother, relaxation lowering intra-villus pressures encouraging water entry from the mother.

These observations led to the concept that transplacental water movement may not be controlled by passive local placental osmotic and hydrostatic phenomena but rather is under active control by the fetus. The major objection to such an hypothesis is that there is no placental innervation connecting the fetus to placenta and any hormonal messenger that could constrict or dilate placental vessels could also disturb fetal hydrostatic function as much as placental. In fact there are several examples of fetal and sub-chorial placental vessels reacting differently to the same hormones [13]. Embryologically, fetal and placental circulations arise independently then unite when embryonic vessels spread over the chorionic plate, making connections to placental villus

Figure 1 Photomicrograph of the human placenta showing well developed vascular smooth muscle in cotyledonal stem arteries and veins (H&E, original magnification 100×). Normalising vein lumen diameter to artery diameter (vein lumen diameter)/(artery external diameter) to compare the contracted diameter of V1 with the relaxed diameter of V2 suggests that these veins can constrict over a ratio of 3:1. Since flow resistance varies with the fourth power of diameter such veins could vary their flow resistance by $3^4 = 81:1$ ratio, much more than is required in the model.
vessels developing below [14]. Vessels of fetal and placental origins have different characteristics [13], including sensitivity to vasoactive polypeptides [13,16]. It is therefore reasonable that differing sensitivities to hormones would allow the subchorial (cotyledonal) part of the placenta to be controlled independently of the supra-chorial and fetal vasculature.

How well is the fetus equipped to respond to undesirable entry or loss of water to the maternal circulation? Postnatally, the Renin-Angiotensin System (RAS) is the primary controller of many aspects of water control. Renin is detectable in the lamb fetal circulation as early as 5 weeks [17], i.e. before development of the final functioning form of the kidney between 9 and 14 weeks. In the fetus control of water load is of greater importance requiring sensing of fetal venous volume rather than renal artery pressure. This is primarily sensed by cardiomyocytes which release Atrial Natururitic Factor (ANF) depending on their stretch. The normal concentration of ANF in the fetus is about 2.5 times that in the adult [18]. If excessive blood volume stretches cardiomyocytes to release more ANF, urine production increases, tending to restore normal volume and immunoneutralising ANF can suppress urine production [19]. An example of the effect of ANF action is severe twin-to-twin transfusion syndrome in which, ANF in the polyhydramniotic recipient may be many times that of the oligohydramniotic donor [20].

Anderson and Faber [21] produced a lamb model of polyhydramnios by chronic infusion of angiotensin-I (Ang-I), which is highly relevant here. Infusion at a rate of 48 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1} \) produced no increased urine flow but 182 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1} \) produced profound polyhydramnios (up to 7 l in 7 days). Fetal arterial pressure rose in proportion to infusion rate but, heart rate, pH, etc. were not significantly disturbed in either case. The hormone apparently induced water to enter from the mother, while causing minimal fetal changes. This demonstrates that there is at least one hormone satisfying the requirement of influencing placental hemodynamics at concentrations that cause minimal or at least complementary changes in fetal hemodynamics.

Summarising, all the components required for fetal control of transplacental water movement are theoretically available. The fetus is equipped to sense deviations in its blood volume, to release hormones in response to abnormal fluid volume which could affect water movement by modifying villus capillary pressure, and so restore optimum water load. It is ethically impossible to manipulate uteroplacental pressures and/or flows to test this hypothesis, so a computer modelling study was set up to examine the feasibility, behaviour, limitations and clinical implications of such a mechanism. Identification of the linking hormone/agents was beyond the scope of this study so the "missing link" hormone was represented by a fictitious hormone "fictensin" to which the placental venous components alone were sensitive.

Methods

An electrical equivalent circuit of the new placental model is shown in Fig. 2. It is driven by a fetal model previously described [22] extended by the addition of a module releasing fictensin as a function of fetal vascular volume. This model is of the iterative type. It is basically a database of some 600 variables in which each iterative cycle calculates the changes that would occur in the next 5 ms and the database updated for the next cycle. The fetal model supplies blood from its abdominal aorta, Paort at the top of Fig. 2, into the placental model's umbilical arteries (Rumba). Blood returns through the fetal model's umbilical vein (Rumbv(extend) + Rumbv(intrafetal)) to the fetal model's umbilical sinus (Pumbsin). Gas and water exchange take place in the terminal villi Rtvc.

Maternal blood (heavy arrows) flows through the intervillus spaces of the inner, middle, and outer layers of the cotyledon (RuiV1, RuiV2, RuiV3), falling in pressure as it goes. In the work described here only the flow resistance of the individual spiral arteries was varied. Increasing a spiral artery resistance reduces flow through the intervillus space of the corresponding cotyledon, and consequently reduces pressure, causing water to move from fetus to mother. Water movement is calculated at each program iteration for each terminal villus taking into account the local intervillus maternal blood pressure. The equation describing the net transvillus pressure driving water transport in each layer of each cotyledon is of the form: 

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P_{\text{xvill}} = P_{\text{tvicap}}/2 + P_{\text{stmv}} + P_{\text{mammo}} - P_{\text{puiv}} - (\text{trpCOP} \cdot \text{PosMat}),
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where \(P_{\text{xvill}}\) is the net transvillus pressure driving water out through the walls of each individual terminal villus, \(P_{\text{tvicap}}\) is the mean pressure drop in the terminal villous system, \(P_{\text{stmv}}\) is the pressure at the entry to the stem vein draining it and \(P_{\text{mammo}}\) is the amniotic pressure produced by tonic uterine wall tension. \(P_{\text{puiv}}\) is added because the fetus and cord are surrounded by amniotic pressure. This has negligible effect on the circulatory differential pressures driving blood around the fetus itself, but must be considered where vessels pass through the
chorionic plate and then act against pressures in the utero-placental space. Puiv is the pressure in the local intervillous space surrounding the villi in that particular layer. The sum of these four is the hydrostatic differential pressure, considered positive if it drives water out of the fetus. To this is added the net colloid osmotic pressure, the bracket term, for that particular layer. \((\text{trpCOP})\) is the colloid osmotic pressure of the villus underlying the syncytium, \(\text{PosMat}\) is the colloid osmotic pressure of the maternal blood. Water transfer is then calculated by applying this pressure \((P_{\text{vill}})\) across the villous surface whose permeability and surface area are combined into a single factor \(L_p\). \(L_p\) for each cotyledon layer was scaled to \(1/81\)th of the primate value \([23]\). Each of these \(81\) water movements were summed, taking into account their direction to obtain net transfer, and summed regardless of direction to obtain net whole placental exchange. This gave a whole placental water exchange similar to the accepted value of \(60\) ml/min \([1]\). The resultant functional control loop is shown in Fig. 3 as it would be expected to respond to a sudden fall in utero-placental flow or pressure.

**Results**

Fig. 4 shows partial screen dumps of one of the model’s monitoring displays, which displays various parameters for one of the three sectors, while the combined model is running. For this figure identical changes in spiral artery resistance were made in all three sectors so that the display represents the placenta as a whole. In (a) all spiral arteries are normal. In (b), one spiral artery has normal resistance, and the third has three times normal. The curved structures represent, from left to right, the inner middle and outer layers

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**Figure 2** The placental model has three sectors, each having a chorionic artery \((R_{\text{chora}})\) and chorionic vein \((R_{\text{chorv}})\). The thick lines indicate the extent of fetally derived vessels that extended down the allantois in the embryo. Within each sector are three cotyledons having a stem artery \((R_{\text{stma}})\) and stem vein \((R_{\text{stmv}})\). Each cotyledon is subdivided into three layers representing, onion like, their inner, middle, and outer regions, (corresponding to the arterial, capillary and venous regions \([30]\). Due to the pressure gradient driving maternal blood through the cotyledon villi water passes from mother to fetus in the core region, and from fetus to mother in the outer layers. This is analogous to the situation in all somatic capillaries \([10]\). The heavy arrows show the path of the maternal circulation through each cotyledon, shown in more detail in the box. Maternal blood from a pressure source representing the uterine arcuate arteries \((\text{Parc})\), passes through radial arteries \((\text{Rrada})\), and a spiral artery \((\text{Rspira})\) to the core of a cotyledon. It then flows through the intervillous spaces of the inner, middle, and outer layers of the cotyledon \((Ruiv1)\), \((Ruiv2)\), \((Ruiv3)\) loosing pressure as it goes, out into the lake \((R_{\text{lake}})\) and uterine vein system back to the maternal IVC.
of each cotyledon, supplied by a stem artery Stma, and drained by a stem vein Stmv. (Their colour code represents oxygenation of blood entering and leaving each layer, used in part one but not part of this study). The numbers in the core region, 19,19,19 in (a) and 19,14,11 in (b) show the mean core pressure produced by spiral artery flow, in mmHg. The other pressures shown 11,11,11 in (a) and 11,9,8 in (b) are the pressures into which maternal blood exits from the outer layers of each cotyledon. These hydrostatic pressures used in calculations of water movement into the fetal circulation in the various layers of the cotyledons and are shown in the panels below. For water transport calculations, the effect of maternal and fetal colloid osmotic pressures are added to produce the total pressure surrounding the villi [10], shown as dark bars in the panels below. Other bars represent the mean hydrostatic pressure in the villous capillaries, PVC, of each layer. The inward and outward flows are equal and opposite so that although there is a fetomaternal exchange of 6.4 ml/min in each direction in each cotyledon the net movement is virtually zero, ("virtually" because there is a continual fluctuation initiated by pulsar-
tility with each heart beat). Over the whole placenta this amounted to an exchange of 68 ml/min (480 ml/h), with a net transfer fluctuating around ±0.1 ml/min.

When the resistance of the spiral arteries of each sector was set to the ratios of 1:1,2:1, and 3:1 of normal (Fig. 4(b)), there was an initial high rapid inward water flow, to which the fetus responded by lowering placental vein resistance and hence villus capillary pressure, until net flow across the whole placenta was once again near zero. (Fig. 1(b)). There are now net flows in all cotyledons but they still sum to zero. Thus, if maternal blood pressure is suddenly changed the momentary water flow is rapidly corrected making the placenta appear impervious. However, if the fetus responds less efficiently (lower loop gain in engineering terms), the correction is not perfect because a greater volume change is required to make the fetus produce enough fictensin to produce the balance pressure. This makes the placenta appear to let a small volume in, i.e. it is slightly permeable. The weaker the fetal response the more permeable the placenta appears to be, but the apparent permeability is actually a measure of the tightness of control, the true permeability is some hundreds of times greater and was not altered in the model.

Discussion

Giving the fetus a fictitious hormone to control various placental resistances reproduced the paradoxical phenomena of a highly water permeable hemochorial placenta resisting water loss or gain, to produce an effective permeability some thousand times less. Fig. 3 summarises the sequence of events in the model following sudden reduction of uteroplacental flow such as might occur in maternal sympathetic outflow in response to an alarming situation. The sudden drop in intervillus pressure leaves intravillus capillary hydro-osmotic pressure higher than that of maternal blood and water leaves the fetal circulation. The drop in fluid volume is sensed by the fetus [1], which reduces fictensin concentration [2], this causes stem veins to relax [3], which in turn reduces intervillus pressure [4]. Momentarily this drop in hydro-osmotic pressure will fall below intervillus pressure causing water to enter the fetal circulation until the correct fetal blood volume is restored. The fetus will then again control the pressure to maintain virtually zero gain or loss of water at the reduced maternal utero-placental blood flow.

The question that follows is of course, is there any evidence that such hormonal control exists, and could it exert an influence on the placenta independently of the fetus’s own internal flow distribution? Anderson and Faber’s [21] model for polyhydramnios reported that Ang-I infusion caused gross polyhydramnios. Recently, another end product of the renin angiotensin system (RAS), angiotensin (1-7) has been identified, derived from Ang-1 or Ang-II, by pathways independent of that producing Ang-II [24], which has been found to produce vasodilation by potentiating the action of Bradykinin. Since conversion of A-I to A (1-7) is carried out by tissue peptisases it only has to be postulated that there is a greater expression of the corresponding Ang to Ang (1-7) peptases in placental venous tissue than in the fetus, for the net effect to be placental venous dilation [25], simultaneously with fetal vascular constriction. It is known that placental vessels do differ in their sensitivity to some hormones even within the placenta itself. Chorionic plate vessels respond to 5-hydroxytryptomine (5-HT), bradykinin (BK) and Angiotensin-II (A-II) in that order, whereas vessels below the chorionic plate respond in the opposite order A-II,BK,5HT [15], indeed MacLean et al. [13] could find no effect of 5-HT on stem vessels at all. Placental veins and arteries have different sensitivities, e.g veins are 10 times as sensitive to endothelin-1 as arteries [13]. This may result from embryonic origins. Placental vessels arise independently from fetal vessels and the two sets only unite when fetal vessels grow down the allantoic stalk, and spread over the inner chorionic surface [14] at about 5 weeks [26]. Chorionic plate vessels originate within the embryonic mass but the chorion itself and structures external to it (villous stems, villi, etc.) are of course extra-embryonic tissues. Preferential conversion of A-1 to A (1-7) in the placenta, but to A-II in the fetus is thus a reasonable possibility given the differing gene imprinting in these two tissues.

We hypothesise that the reaction to reduction in uterine hydrostatic pressure in the Anderson and Faber lamb model (Fig. 3, shown in [ ] brackets) would be increase in Ang-1, and that when the increased Ang-1 reaches vessels passing through the chorion and beyond a large proportion is converted to Ang (1-7). Then gross polyhydramnios at the larger dose resulted from the normal fetal control system being overwhelmed, leaving the placental venous system fully dilated, producing low capillary pressure, and allowing maternal water to enter. The lower dose was within the fetus’ capabilities to compensate and so no polyhydramnios would result. So the lamb model shows that events in the FETAL CHARLOTTE model are at least paralleled in vivo. It must now be considered how
far this lamb model can be considered valid to the human case in view of their very different placental construction.

Site of water transfer

Although there are extra sites of materno-fetal water exchange in the ovine conceptus, we assume that the dominant site is through the placental cotyledons. There are no true villi in the sheep placenta. It is of the epitheliocorial type in which there is no breakdown of the uterine or fetal epithelium, sheets of capillary networks simply become closely apposed separated by their two epithelial layers (see Figs. 5, 6). In the human hemochorial placenta the intravillus capillaries are surrounded by maternal blood, and if the uterine pressure exceeds intravillus capillary pressure they must collapse, becoming Starling Resistance elements. Thus, hemochorial placentae such as those of humans and primates are essentially low pressure placentae; (monkey spiral artery outlet pressure of 12.5 mmHg; [9,27]. In the epitheliocorial types, such as in ruminants, hydrostatic pressure communication has to be indirect via interstitial water pressure and so appears reduced, and nearly the full arterial pressure is available to drive blood through the extensive sheets. Placental capillary inlet pressures were measured at 40 mmHg in the sheep [28]. Another important difference is the effective pore size of the tissue path separating the two bloods. The lamb placenta blocks simple diffusion transit to molecules greater than 0.42 nm radius, whereas the human placenta allows molecules up to 20 nm radius to pass freely [29]. This means that the colloid osmotic pressure difference developed across the separating tissue will be much higher in the lamb than in the human or primate. Thus, the hemochorial configuration of human placenta confers greater transfer efficiency at the expense of greater vulnerability to intervillus hydrostatic pressure fluctuations, while the lamb is more vulnerable to changes in blood ionic content. The described hypothetical mechanism would be suitable.
to both types, producing correcting pressures in proportion to their vulnerability.

**Boundary junction between vessels of embryonic and extra-embryonic derivation**

Reverse hormone sensitivity patterns extend from the exchange surfaces into the villus stem vessels [13,15], which are situated immediately below the vessels penetrating the chorion. If this basic system is common to all placental animals to some degree, this would suggest that a boundary exists where vessels penetrate the chorion, we describe this as the transchorionic boundary and such vessels as transchorionic vessels. It must be determined which lamb placental vessels would correspond to the villus stem vessels in the human placenta? We suggest that where the distributing vessels upon entering each caruncle in the sheep placenta should show similar behaviour to human stem vessels. If this represents what happens in vivo it means that the high water permeabilities observed in in vitro experiments, which agree with the DO2 isotope in vivo studies, are true and not due to preparation trauma as has been suggested. The permeabilities measured in in vivo loading experiments are a measure of the performance of the closed loop system. If the fetal volume sensitivity were infinite, any water transfer in either direction would be exactly corrected and the placenta would appear impermeable, even though water was entering the fetus quite freely from the cotyledonary core terminal villi and leaving from those in the outer cotyledonary shell. In reality, in vivo control will be less than perfect, and the working effective permeability will always be finite. Hence these model studies suggest that the low permeability observed in in vivo water loading experiments is not true permeability, it is a measure of the efficiency of the fetoplacental water regulating control capability.

**Clinical implications**

There are limits to the range of pressures the fetus can produce by vasoconstriction or relaxation. If maternal pressure exceeds the upper limit the fetus cannot defend itself against increased intervillus pressure and the fetus floods, stimulating an ANF → polyuria → polyhydramnios sequence and edema. In the opposite direction, the fetus can only lower intervillus mean pressure by removing the normal constrictive agent and/or the normal vagal tone. If the opposing maternal and fetal COPs demand a lower pressure than the fetus can produce, intervillus pressure will drive water out to the mother, leading to fetal hemoconcentration and oligohydramnios. The resulting increase in fetal COP may retain some water, but the same increased COP will be applied to every organ in the body, impairing their function.

**References**


