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John Hunter's Unsung Contribution to Obstetric Medicine and its Role in the Diagnosis and Management of Fetomaternal Haemorrhage.

One might find it initially unconventional for an essay on the subject of John Hunter to expound his particular contributions to obstetric medicine; especially in light of both his widely celebrated legacies to vascular medicine and scientific surgery, and the ubiquitous reverence that his brother, William Hunter, had received for his pioneering research in obstetric anatomy, documented in *The Anatomy of the Human Gravid Uterus* (1774). However, it has been widely established - and documented by both Kaya & Sindel (2016), and Wagoner (2017) - that in fact, John Hunter arguably made one of the most important yet poorly credited observations in obstetric medicine to date: the separation of the maternal and foetal circulations. In 1837, while describing the vascular anatomy and physiology of the maternal gravid specimen and comparing its features with that of the foetus, he reflected that "placental intercommunication between the foetus and the mother, in the human subject and Quadrumana, is carried on by the contact of the foetal capillaries with maternal extravasated blood" (Hunter, 1837, p. 70) , insisting that the contribution of maternal blood to the placenta is "detached from the common circulation of the mother" (Hunter, 1837, p.67) - which was entirely contrary to the theories of his contemporaries. This essay aims to accentuate the lasting relevance of John Hunter's placental anatomical observations in the diagnosis and management of fetomaternal haemorrhage and its subsequent foetal effects.

As determined by Brown (1963), it is largely expected that in at least 50% of women within 24 hours postpartum, there is a small yet measurable transplacental bleed of foetal erythrocytes into the maternal circulation. The clinical requirements of what constitutes a significant fetomaternal haemorrhage have since been widely debated; however in concordance with de Almeida and Bowman's (1994) findings, this essay defines a massive fetomaternal transplacental haemorrhage as being greater than 80 ml, wherein a range of complications including foetal distress, severe neonatal anaemia and unexplained foetal death had been precipitated. The pathophysiology of fetomaternal haemorrhage, as stated in Singh and Swanson's (2014) review of the literature, usually originates from a breach in the placental trophoblast, of which the main established predictors are abruptio placentae, amniocentesis and abdominal trauma; wherein the comparatively higher pressure of foetal circulation pushes foetal erythrocytes into the intervillous space. These erythrocytes then enter the maternal circulation, and ABO group compatibility perpetuates the severity of the haemorrhage.

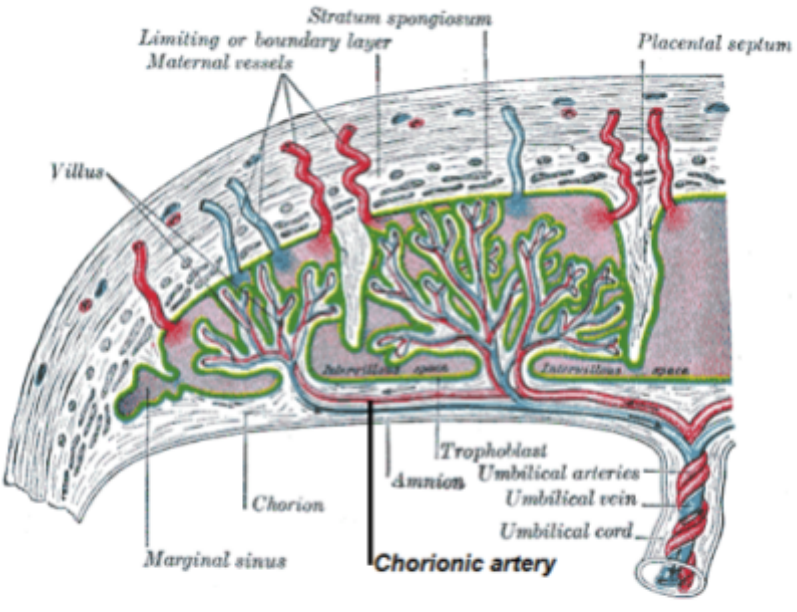

Figure 1: A diagram of the anatomy of the chorionic villi and maternal vessels.

Causative Factors of FMH and Diagnosis

Massive fetomaternal haemorrhage, being a relatively uncommon and often unexpected occurrence, is often retrospectively diagnosed through two main investigations: the Kleihauer-Betke (KB) acid elution test and flow cytometry. In Wylie and D'Alton's (2010) comparison of these diagnostic investigations, the KB acid elution test - wherein HbF

erythrocytes are stained red with erythrosine B - requires a minimum of 10,000 erythrocytes to be counted, which increases both the turnaround time and the likelihood of fetomaternal hemorrhage underestimation due to cell staining failure. Alternatively, flow cytometry offers an increased diagnostic precision through the automated process of fluorescence detection of HbF-bound monoclonal antibodies. Flow cytometry is particularly pertinent to John Hunter's placental anatomical observation, because Hunter postulated that in the case of foetal capillaries, "as the uterus increases in every part of its surface during the time of uterine gestation, we must suppose that...by the elongation of those vessels of the foetus in every direction this substance should likewise be increased in every direction" (Hunter, 1837, p. 66), which refers to normal chorionic villous maturation, as shown in **Figure 1.**

As Turowski and Vogel (2018) explain, it is important for normal villous maturation to occur respective to gestational age in order to accommodate dynamic adaptation processes in light of the changing nutritional and oxygen demands of the foetus. However, in a study by Lewis *et al*. (2017) that aimed to detect placental pathologic features in fetomaternal haemorrhage with flow cytometry, the results demonstrated that there was a positive correlation between fetomaternal haemorrhage severity and the incidence of villous dysmaturity, immaturity and oedema. This finding corroborates with Hunter's aforementioned suggestion that in foetal development, chorionic villous maturation from intermediate villi to mature intermediate and terminal villi should be proportional to the progression of the gestational period; otherwise disorders of villous maturation that disrupt the vascular integrity of the placenta can become causative factors of fetomaternal haemorrhage.

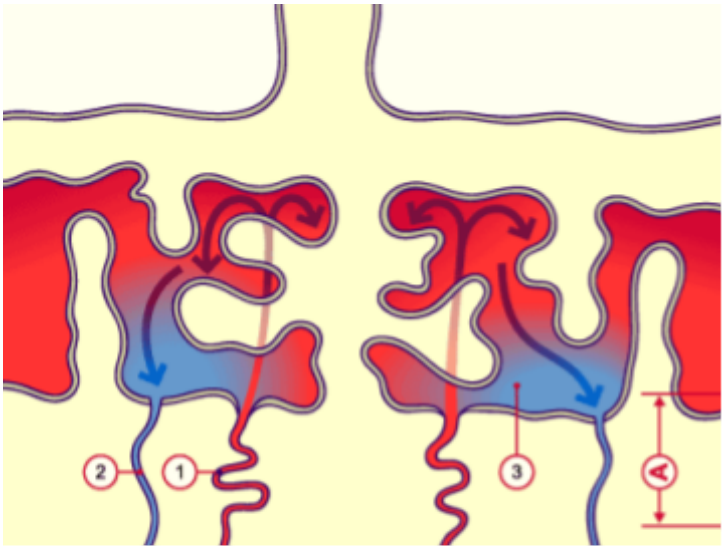

Figure 2: The maternal circulation system. The labelling is as such that (1) refers to the uterine spiral arteries, (2) the uterine veins, (3) the intervillous spaces with extravasated maternal blood and (A) the basal plate.

Another causative factor of fetomaternal haemorrhage is abruptio placentae. In Hunter's explanation of the placental structure, he describes that "the blood of the mother must pass freely into the substance of the placenta ....the turgidity of which will assist to squeeze the blood into the mouths of the veins of the uterus" (Hunter, 1837, p. 67), which is a reference to the dynamics of the maternal blood as it travels from the uterine spiral arteries into the intervillous spaces and eventually back down to the uterine veins. This vascular anatomy is shown in more detail in **Figure 2**. Furthermore, he specifically identifies and describes the course of the uterine arteries as passing "through the decidua without ramifying...making two or three close spiral turns upon themselves", proceeding to "open at once into its spongy substance without any diminution of size and without passing beyond the surface"(Hunter, 1837, p. 66).

This information is important in our understanding of the pathophysiological mechanism of abruptio placentae, because, as described by Schmidt and Raines (2018); during abruptio placentae, the vascular networks - mainly comprising of the spiral arteries and uterine veins - become compromised and tear away from the placenta, which contributes to a profuse, accumulative bleed. One can therefore deduce that, given

Hunter's observation on the full placenta's turgidity playing a role in maintenance of the utero-placental circulation system, that during abruptio placentae, the loss of turgidity in the intervillous spaces as a result of the bleeding allows for the unregulated transference of foetal erythrocytes across the trophoblast layer into intervillous spaces, due to the aforementioned comparatively higher foetal blood pressure.

Management

Solomonia, Playforth *et al*. describe, in their 2011 case and literature review, that the symptomal presentation of the affected infant - in the 87.5% cases that did not result in unexpected stillbirth - is largely non-specific; however Solomonia, Playforth *et al*. (2011), Wylie and D'Alton (2010) and de Almeida and Bowman (1994) all concur that the main triad of late-stage presentations associated with fetomaternal haemorrhage are decreased foetal movement, sinusoidal heart rate and non-immune hydrops fetalis - all three of which are also symptomal of the severe and uncompensated neonatal anaemia associated with fetomaternal haemorrhage. de Almeida and Bowman describe that the most appropriate decision in the management of fetomaternal haemorrhage is the investigation of foetal distress and either neonatal transfusion for a term foetus, or cord blood sampling and intravascular transfusion for a premature foetus. Intravascular intrauterine transfusion is of particular interest, because, as recounted by Lindenberg, van Kamp et al. (2014), it is known to be one of the most successful invasive treatments - not only for severe foetal anaemia, but in foetal medicine as a whole.

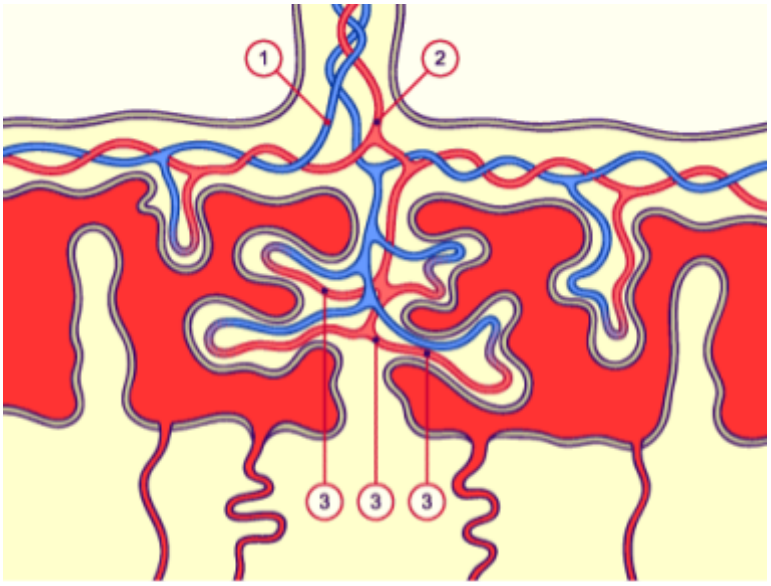

Figure 3: A diagram demonstrating the uteroplacental circulation system in full. In terms of labelling, (1) refers to the umbilical arteries from the foetus, (2) the umbilical veins and (3) the foetal capillaries within the chorionic villi.

In Bock, Bang and Trolle's 1982 description of ultrasound-guided foetal intravenous transfusion, a guide needle is inserted through the foetal abdomen and into the hepatic part of the umbilical vein, wherein a fine needle is introduced into the lumen in preparation for transfusion. One can appreciate, when considering **Figure 3**, that this procedure requires a precise knowledge of the anatomy of the utero-placental circulation; and, in fact, it was John Hunter who initially described the distinct structures that constituted the foetal communication with the placenta. He observed that:

> The arteries from the foetus pass out to a considerable length, under the name of the umbilical arteries and when they arrive at the placenta ramify upon its surface, sending into its substance branches which pass through it, and divide...till at last they terminate in veins...and end in one, which at last communicates with the proper circulation of the foetus. (Hunter, 1837, p. 67)

Without this fundamental anatomical observation, the development and use of intravascular intrauterine transfusion to manage severe foetal anemia may not have surpassed its predecessor, intraperitoneal transfusion, which was found by Bock *et al.* to have not only poor results in the cases of hydrops fetalis and low gestational

age, but also to have a 25-70% foetal survival rate. Lindenberg, van Kamp *et al.* (2014) further attest to the comparative success of intravascular intrauterine transfusion, noting that IUT treatment after 32/40wks may be safer than procedures performed in early gestation, and can prolong gestation until term, thus greatly improving the prognosis for foetuses that may be at risk of suffering the effects of severe neonatal anaemia as a result of fetomaternal haemorrhage.

Conclusion

In conclusion, it is clear that without Dr. John Hunter's extensive and progressive observations within placental anatomy - underlined by his revolutionary theory regarding the separation of the maternal and foetal circulation - we would not have been able to both enhance our clinical understanding of fetomaternal haemorrhage and other grave disorders relating to the disruption of placental vascular integrity, and ameliorate techniques such as intravascular intrauterine transfusion for the management of severe neonatal anaemia and its complications. Although Hunter is already ubiquitously lauded as an outstanding and innovative surgeon with a profound impact on vascular medicine, it is imperative that as clinicians, let alone as prospective or established obstetricians and paediatricians, we must accredit him with providing unmatched resources in helping us to overcome the scourges of maternal mortality and foetal mortality in relation to obstetric haemorrhage as a result of placental vascular disruption or abnormality.

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Bibliography

Figure 1: Chorionic artery (2020), Diagram, Medicine Libre Texts, Accessed 29/08/2020 <https://med.libretexts.org/Bookshelves/Anatomy_and_Physiology/Book%3A_Anatomy_and_Physiology_(Boundless)/27%3A_Human_Development_and_Pregnancy/27.4%3A_Third_Week_of_Development/27.4E%3A_Chorionic_Villi_and_Placental_Development>

Figure 2: Maternal circulation system (2020), Diagram, Embryology.ch (Universities of Friborg, Lausanne and Bern), Accessed 29/08/20. <http://www.embryology.ch/anglais/fplacenta/circulplac01.html>

Figure 3: Utero-placental circulation system (2020), Diagram, Embryology.ch (Universities of Friborg, Lausanne and Bern), Accessed 29/08/20. <http://www.embryology.ch/anglais/fplacenta/circulplac01.html>

Bang, J., Bock, J. E. and Trolle, D. (1982) '*Ultrasound-guided fetal intravenous transfusion for severe rhesus haemolytic disease*', British Medical Journal (Clinical research ed.). Br Med J (Clin Res Ed), 284(6313), pp. 373–374. doi: 10.1136/bmj.284.6313.373.

Brown, E. S. (1963) 'Foetal Erythrocytes in the Maternal Circulation', *British Medical Journal*. England: British Medical Association, 1(5336), pp. 1000–1001. doi: 10.1136/bmj.1.5336.1000

de Almeida, V. and Bowman, J. M. (1994) 'Massive Fetomaternal Hemorrhage: Manitoba Experience', *Obstetrics and gynecology (New York. 1953)*. United States: The American College of Obstetricians and Gynecologists, 83(3), pp. 323–328.

Hunter, J. (1837) '*The Works Of John Hunter F.R.S. With Notes: Volume 4*.' Longman, Rees, Orme, Brown, Green, and Longman, pp.66-70.

Kaya, Y. and Sindel, A. (2016) 'John Hunter (1728–1793) and his legacy to science', Child's Nervous System. Springer Verlag, pp. 1015–1017. doi: 10.1007/s00381-015-2852-x.

Lewis, N. E., Marszalek, L. and Ernst, L. M. (2017) 'Placental pathologic features in fetomaternal hemorrhage detected by flow cytometry', Pediatric and Developmental Pathology. SAGE Publications Ltd, 20(2), pp. 142–151. doi: 10.1177/1093526616687652.

Lindenburg, I. T. M., van Kamp, I. L. and Oepkes, D. (2014) 'Intrauterine Blood Transfusion: Current Indications and Associated Risks', Fetal Diagnosis and Therapy. S. Karger AG, 36(4), pp. 263–271. doi: 10.1159/000362812.

Schmidt, P. and Raines, D. A. (2018) Placental Abruption (Abruptio Placentae), StatPearls. StatPearls Publishing. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29493960 (Accessed: 31 August 2020).

Bibliography (continued)

Solomonia, N., Playforth, K. and Reynolds, E. (2011) 'Fetal-Maternal Hemorrhage: A Case and Literature Review', American Journal of Perinatology Reports. Georg Thieme Verlag KG, 02(01), pp. 007–014. doi: 10.1055/s-0031-1296028.

Singh, P. M. and Swanson, T. (2018) 'Management of major obstetric haemorrhage', Indian Journal of Anaesthesia. Indian Society of Anaesthetists, pp. 698–703. doi: 10.4103/ija.IJA_448_18.

Turowski, G. and Vogel, M. (2018) 'Re-view and view on maturation disorders in the placenta', APMIS. Blackwell Munksgaard, 126(7), pp. 602–612. doi: 10.1111/apm.12858.

Wagoner, N., 2017. *John Hunter (1728–1793) | The Embryo Project Encyclopedia*. [online] Embryo.asu.edu. Available at: <https://embryo.asu.edu/pages/john-hunter-1728-1793> [Accessed 31 August 2020].

Wylie, B. J. and D'Alton, M. E. (2010) 'Fetomaternal hemorrhage', Obstetrics and Gynecology, pp. 1039–1051. doi: 10.1097/AOG.0b013e3181da7929.