Authors:
Rachel Anne Muscat Baron &
Abigail Micallef

Reviewers:
Dr. Edith Said
Prof. Charles Savona Ventura

The Pathophysiology of Hydrops Fetalis

Introduction

Hydrops fetalis (HF) is a condition that develops during foetal life. It is defined as the abnormal accumulation of fluid in at least two serous cavities and/or within the soft tissues of the foetus. This includes ascites, pericardial effusion, skin oedema and pleural effusion (1,2).

Studies have shown that the current incidence of HF is 1.80 per 1,000 total births with a mortality rate as high as 50% to this day, despite the advancements made in foetal intervention and neonatal care (3–5)

There are two main causes of HF, immune and non-immune. The immune cause of HF was previously the major cause of HF, however, due to the introduction of preventative medicine, there has been a marked reduction of cases in the western world, which have now been surpassed by the non-immune causes (6),(7,8).

Immune causes are due to antigen-antibody incompatibility of the mother and the developing foetus, leading to maternal immunological response to the paternally inherited antigens of the foetus (9). Non-immune causes include cardiovascular disorders, lymphatic dysplasias, haematological abnormalities, chromosomal imbalances, infections, conditions during pregnancy, metabolic disorders, tumours, and idiopathic ones. The pathophysiology leading to non-immune hydrops fetalis (NIHF) hence, depends on the cause.

List of Abbreviations

cGMP	Cyclic guanosine monophosphate
HF	Hydrops Fetalis
IHF	Immune hydrops fetalis
NIHF	Non-immune hydrops fetalis
RBCs	Red Blood Cells

Transport of Foetal Fluids

The foetus has a high risk of fluid accumulation due to the physiology of the microcirculatory and lymphatic system during development (10). Both the capillary filtration coefficient and reflection coefficient, as in the Starling Principle, imply that the endothelium is an important structure in determining the net movement of fluid between the different compartments (10). Damage to the glycocalyx makes the capillary endothelium more permeable (11,12). In such a case, due to a smaller driving force, water retains in interstitial space resulting in NIHF. Presence of high glucose level brings an increase in metabolic rate, which without rising levels of oxygen results in foetal hypoxia, acidosis, as well as, severe accumulation of fluid (11).

Lymphatic Return

The lymphatic system regulates the return of solutes and extracellular fluid to the circulation, and functions in immune cell trafficking (13). This can occur after the sixth embryonic week, once lymphangiogenesis has taken place (14). The rate of fluid extravasation and lymphatic return must be approximately equal, otherwise, a decline in lymphatic return leaves foetal oedema due to interstitial space expansion, and eventually hydrops (11,15). HF can also develop in cases of drastic reduction in lymphatic flow due to rise in foetal venous pressure (11).

Foetal Transmission to Amniotic Fluid

Amniotic fluid is the product of foetal skin transudation made approximately from the tenth to the twentieth week, such that its composition is similar to that of the foetal extracellular fluid (11,16). During this time, keratinisation of foetal membranes has not yet occurred hence, water and solute transport can occur by diffusion. The syncytiotrophoblast and the placental villi contain aquaporin 4, contributing to water transport into the amniotic sac too (17). NIHF can therefore also develop from the incorrect function of these aquaporins (11).

In the second half of pregnancy, amniotic fluid is synthesised by the lungs and urine of the foetus (11),(16). Placental or renal malfunctions therefore, likely change the fluid balance of the foetus and cause NIHF (11).

Isoimmunisation

Isoimmunisation is the process whereby antibodies form against antigens which are incompatible with those of another individual (7,8). This process may lead to the development of IHF, previously the major cause of HF, however, due to advancements in preventative medicine, this has been narrowed down to less than 10% of all HF etiologies (5), (6),(7,8).

The most common form is that of Rh incompatibility which occurs when the blood of negative Rh mothers is exposed to the positive Rh factor present in the developing foetus who would have inherited the positive Rh factor from the father (7,8),(18).

Rhesus factor is an antigen, which is a protein found on the cell surface membrane of red blood cells (RBCs). It is essential to determine whether the father is homozygous or heterozygous for the antigen to analyse the risk the foetus has in developing the haemolytic disease of the foetus (7,9,18)). Being that the inheritance of the positive factor is dominant, although the mother is negative for the antigen, the offspring could inherit the factor from the heterozygous or homozygous father (7,9,18).

Destruction of the placental barrier will cause fetomaternal haemorrhage which allows foetal blood to enter the maternal circulation (7,9,18)). Once the foreign antigens gain entry into the maternal circulation, they are able to incite the reticuloendothelial system reaction which identifies the foreign antigen and presents the antigens to the humoral immune system. The specialised B lymphocytes forming part of the humoral system recognises the antigen and mounts an immune response against these cells by synthesising IgM and IgG antibodies (7,9,18).

The initial response of the maternal immune system results in the formation of a low level of IgM antibodies. During the first pregnancy, the level tends to be insignificant and is unlikely to have an effect on the foetus as the humoral immune system requires time to elicit an effective antibody response (7,9).

The IgM antibodies are themselves too large to cross the placental barrier, however, they are able to form IgG antibodies that are smaller and able to cross (7,9,18). Hence, during the following Rh-D positive pregnancy, due to re-exposure to the antigen, the primary memory B cells made against these antigens will increase the IgG antibodies synthesised, the booster response. The IgG antibodies will cross the placenta by binding to the Fcy receptors of the syncytiotrophoblasts (7,9). The RBC-antibody bound cells are trapped within the foetal spleen and consequently destroyed by macrophages (7,9).

Endothelial Involvement

Studies have shown that the foetal plasma of alloimmunized pregnancies would have a decreased amount of cyclic guanosine monophosphate (cGMP), which is complicated by hydrops fetalis. The decrease in cGMP leads to damage of the foetal vascular endothelial cells, which thus leads to a decreased nitric oxide production by the

endothelial cells. This decrease can cause severe endothelial cell injury which is thought to lead to the development of ascites and oedema (19).

Foetal Anaemia

One of the major complications caused by Rh incompatibility is haemolysis. The decreased number of RBCs caused by haemolysis may result in hyperbilirubinemia or/and anaemia, therefore affecting morbidity and mortality (20,21). Ultrasonographically, this is noted by hepatosplenomegaly as well as pleural effusion, pericardial effusion, ascites, subcutaneous and scalp oedema. Furthermore, due to the decreased oxygen supply to the cells, placentomegaly may result, as a compensatory mechanism (7).

Circulation in the Foetus

Many of the congenital cardiac anomalies and disorders existing, change the flow volume of blood in the outflow tract and are the leading cause of cardiogenic NIHF (11,22). Owing to the ductus arteriosus, blood can pass from the pulmonary trunk to the aortic isthmus. Obstruction to this patent blood vessel can occur due to low partial pressure of oxygen, local nitric oxide production and high prostaglandin concentration, all of which reduce its patency (11,23).

In Due to resultant low oxygen levels of blood in the pulmonary circulation, pulmonary vessels constrict and increase their myogenic tone. This enhances the pulmonary vascular resistance, preventing rise in pulmonary artery pressure and inhibiting increase in blood flow at the left atrium (11,22).

turn, these maintain the foramen ovale patent, such that at diastole, blood flows from the right to the left side of the heart, rather than entering the pulmonary circulation. Simultaneously, abnormal left atrial pressure and a narrow foramen ovale decrease blood entering the left ventricle (22). This develops decreased ventricular compliance and hence, high end-diastolic volume and congestive heart failure. A high afterload also results in a small cardiac output. Resultant increase in pulmonary blood flow induces pulmonary lymphoedema, and this complicates as hydrothorax and NIHF (11). As explained by Starling's Principle, raised central venous pressure also leads to hydrops due to minimal fluid reabsorption (11).

Development of Foetal Hypoxia

Foetal asphyxia or heart failure promotes the retention of fluid resulting in polyhydramnios and NIHF. Furthermore, angiotensin receptors in the umbilical artery epithelium induce

vasoconstriction, such that the foetus retains more water and salt from the placenta, causing renal impairment. Oliguria and anuria augment hydrops (11).

At early gestation, the ductus venosus is still not responsive to catecholamines and so, smooth muscle layers of the intra-hepatic veins are stimulated to vasoconstrict.

This may result in liver failure due to hypoxic damage, such that less albumin is synthesised; lowering oncotic pressure inside the capillary and enhancing NIHF formation (11). Atrial natriuretic peptide is also released from atrial myocytes when central venous pressure is high and ventricular distension occurs (24). This lowers blood pressure by inducing vasodilation and increasing capillary permeability (25).

Conclusion

It is evident that there is substantial knowledge about the pathophysiology of HF. Furthermore, the importance of understanding this is essential for the advancements in the treatment of the condition. Being that the etiologies of HF are diverse, this makes finding a treatment highly dependent on the diagnosis of the cause in a timely manner (4).

The pathophysiologies of certain causes of NIHF are still unknown, thus making treating such a condition significantly harder. Although advancements made have resulted in a significant decrease in mortality, namely in regards to IHF, HF is still notable, and thus, research on this front is still highly sought after (4).

References

1. Trainor B, Tubman R. The emerging pattern of hydrops fetalis--incidence, aetiology and management. Ulster Med J. 2006 Sep;75(3):185–6.

2. Bukowski R, Saade GR. Hydrops fetalis. Clin Perinatol. 2000 Dec;27(4):1007–31.

3. Ratanasiri T, Komwilaisak R, Sittivech A, Kleebkeaw P, Seejorn K. Incidence, causes and pregnancy outcomes of hydrops fetalis at Srinagarind Hospital, 1996-2005: a 10-year review. J Med Assoc Thai. 2009 May;92(5):594–9.

4. Nassr AA, Ness A, Hosseinzadeh P, Salmanian B, Espinoza J, Berger V, et al. Outcome and treatment of antenatally diagnosed nonimmune hydrops fetalis. Fetal Diagn Ther. 2018;43(2):123–8.

5. Takci S, Gharibzadeh M, Yurdakok M, Ozyuncu O, Korkmaz A, Akcoren Z, et al. Etiology and outcome of hydrops fetalis: report of 62 cases. Pediatr Neonatol. 2014 Apr;55(2):108–13.

6. Singla S, Kumar S, Roy KK, Sharma JB, Kachhawa G. Severe hydrops in the infant of a Rhesus D-positive mother due to anti-c antibodies diagnosed antenatally: a case report. J Med Case Reports. 2010 Feb 18;4:57.

7. Agarwal K, Rana A, Ravi AK. Treatment and prevention of rh isoimmunization. J Fetal Med. 2014 Jun;1(2):81–8.

8. Liumbruno GM, D'Alessandro A, Rea F, Piccinini V, Catalano L, Calizzani G, et al. The role of antenatal immunoprophylaxis in the prevention of maternal-foetal anti-Rh(D) alloimmunisation. Blood Transfus. 2010 Jan;8(1):8–16.

9. Snowise S, Johnson A. Immune Hydrops Fetalis. Obstetric imaging: fetal diagnosis and care. Elsevier; 2018. p. 526-532.e1.

10. Apkon M. Pathophysiology of hydrops fetalis. Semin Perinatol. 1995 Dec;19(6):437–46.

11. Bellini C, Hennekam RCM. Non-immune hydrops fetalis: a short review of etiology and pathophysiology. Am J Med Genet A. 2012 Mar;158A(3):597–605.

12. Butler MJ, Down CJ, Foster RR, Satchell SC. The pathological relevance of increased endothelial glycocalyx permeability. Am J Pathol. 2020 Feb 6;190(4):742–51.

13. Bernier-Latmani J, Sabine A, Petrova TV. Development and differentiation of the lymphatic vascular system. In: Schmidt MH, Liebner S, editors. Endothelial signaling in development and disease. New York, NY: Springer New York; 2015. p. 115–33.

14. Tammela T, Alitalo K. Lymphangiogenesis: Molecular mechanisms and future promise. Cell. 2010 Feb 19;140(4):460–76.

15. Moore JE, Bertram CD. Lymphatic System Flows. Annu Rev Fluid Mech. 2018 Jan;50:459–82.

16. Underwood MA, Gilbert WM, Sherman MP. Amniotic fluid: not just fetal urine anymore. J Perinatol. 2005 May;25(5):341–8.

17. Hua Y, Jiang W, Zhang W, Shen Q, Chen M, Zhu X. Expression and significance of aquaporins during pregnancy. Front Biosci (Landmark Ed). 2013 Jun 1;18:1373–83.

18. Krywko DM, Jamal Z, Shunkwiler SM. Kleihauer Betke Test. StatPearls. Treasure Island (FL): StatPearls Publishing; 2020.

19. De Groot CJ, Oepkes D, Egberts J, Kanhai HH. Evidence of endothelium involvement in the pathophysiology of hydrops fetalis? Early Hum Dev. 2000 Mar;57(3):205–9.

20. Basu S, Kaur R, Kaur G. Hemolytic disease of the fetus and newborn: Current trends and perspectives. Asian J Transfus Sci. 2011 Jan;5(1):3–7.

21. Pegoraro V, Urbinati D, Visser GHA, Di Renzo GC, Zipursky A, Stotler BA, et al. Hemolytic disease of the fetus and newborn due to Rh(D) incompatibility: A preventable disease that still produces significant morbidity and mortality in children. PLoS ONE. 2020 Jul 20;15(7):e0235807.

22. Rudolph AM. Congenital cardiovascular malformations and the fetal circulation. Arch Dis Child Fetal Neonatal Ed. 2010 Mar;95(2):F132-6.

23. Gournay V. The ductus arteriosus: physiology, regulation, and functional and congenital anomalies. Arch Cardiovasc Dis. 2011 Nov;104(11):578–85.

24. Hofstaetter C, Gudmundsson S. Venous Doppler in the evaluation of fetal hydrops. Obstet Gynecol Int. 2010 May 5;2010:430157.

25. Thakur V, Fouron J-C, Mertens L, Jaeggi ET. Diagnosis and management of fetal heart failure. Can J Cardiol. 2013 Jul;29(7):759–67.