Review Article

THE INFLUENCE OF PLACENTAL MICROBIOMES ON IMMUNOLOGY AND ALLERGY AND THE EFFECT OF PLACENTAL INFLAMMATION ON IMMUNITY IN NEWBORNS

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ABSTRACT

Stillbirth remains a global adverse pregnancy outcome affecting approximately three million pregnancies each year. Most stillbirths that occur in low- and middle-income countries are reported to be as a result of infections, which account for approximately 50% of deaths.[1] In South Africa, despite a substantial decrease in infant mortality rates over the past decade, in 2018 the infant mortality rate was still 36.4 per 1 000 live births.[2] The protection of the newborn against infection is dependent upon the innate immune system as their capacity for adaptive immune response is limited. Infants are susceptible to infection as a result of insufficient memory-effector B-cells and effector-memory T-cells. During pregnancy, placental infection can lead to the transfer of an antigen to the foetus, which results either in infection of the foetus (sepsis) or in a foetal immune response,[3] with increased risk of preterm birth, neurological sequelae or stillbirth.[1] During pregnancy there is cross-over of the maternal gut microbiome to the placenta and into the amniotic fluid. This exposure to bacteria plays a role in the development of the immune system and, in turn, the subsequent quality of life. It has been postulated that this initial bacterial exposure has a direct impact on the immune tolerance and the response of the child to allergies and autoimmune diseases.[4] The placental microbiome may certainly play a role in the aetiology of diseases experienced by children and adults.

Key words: placental microbiome, immunity, stillbirth, chorioamnionitis, villitis

ANATOMY AND FUNCTION OF THE PLACENTA

The placenta is a temporary organ of both maternal and foetal origin formed during pregnancy. It is an oval-shaped organ consisting of the foetal membranes: chorion and amnion (forming the amniotic sac enclosing the foetus), the parenchyma (contains connective tissue, chorionic villi and trophoblast) and decidua capsularis (close to the maternal side).[5]

The trophoblast comprises placental cells that permit the transfer of oxygen and carbon dioxide and the removal of waste between the foetus and the maternal blood. The placenta is responsible for metabolising many products which are exchanged between the maternal and the foetal interface. The sole purpose of the placenta is to support the growth and developmental requirements of the foetus during gestation.[6,7]

PLACENTAL INFLAMMATION

The consequences of placental inflammation are severe and cause significant foetal and neonatal morbidity and mortality.[8] Preterm birth is a major complication of inflammation associated with the foetal inflammatory response syndrome (FIRS). FIRS can lead to cardiorespiratory, neurological and renal complications that adversely influence the quality of life (QoL), should the neonate survive.[9]

Inflammation may reach the placenta via several routes. The commonest of these routes ascends from the lower female

genital/urinary tract, but is contiguous with the uterus or fallopian tubes; here, haematogenous and iatrogenic diagnostic/therapeutic procedures may occur. Inflammation of the chorioamnion and decidua basalis is referred to as chorioamnionitis and deciduitis. Inflammation of the villous tree is known as villitis.[10]

The origin of placental inflammation lies in either an organism (viral, bacterial or fungal), a host immune response or an unknown agent.[10] During a chronic inflammatory response, infiltration of various cells into the different placental compartments is observed. An increased presence of lymphocytes and plasma cells is seen in the decidua basalis. This is accompanied by a mixture of lymphocytes and eosinophils in the chorioamnion together with lymphocytes and histocytes in the villous tree and occasionally in the intervillous space (intervillositis).[11]

CHORIOAMNIONITIS

Chorioamnionitis (CA) is usually an ascending infection caused most commonly by bacteria and is estimated to be present in approximately 2–4% of term pregnancies.[12] Stillbirths as a result of CA may be underestimated. Many studies include foetal-death statistics only after 28 weeks of pregnancy, and infection is not recorded as a frequent cause of stillbirth prior to 28 weeks. However, the placenta is rarely examined in developing countries and the cause is not therefore determined.[1] Common bacterial infections are due to *Mycoplasma*, *Ureaplasma* species and *Streptococcus* group B, which originate in the urogenital tract.[13]

These bacterial infections cause inflammation of the chorion and the amnion (membranes). This results in an inflammatory response of maternal and/or foetal origin.[12] In this chain of events endotoxins and exotoxins are released from bacteria which activate transcription factors and signal transducers and activators of transcription (STAT); these in turn signal the production of cytokines and chemokines (TNF, IL-1, IL-6, IL-8). These cytokines and chemokines generate arachidonic acid through the activation of phospholipases, arachidonic acid – Pg H2 – Pg E2 and Pg F2 alpha. These produce metalloproteases that induce uterine muscle contraction, possibly leading to uterine muscle contraction with consequent preterm labour.

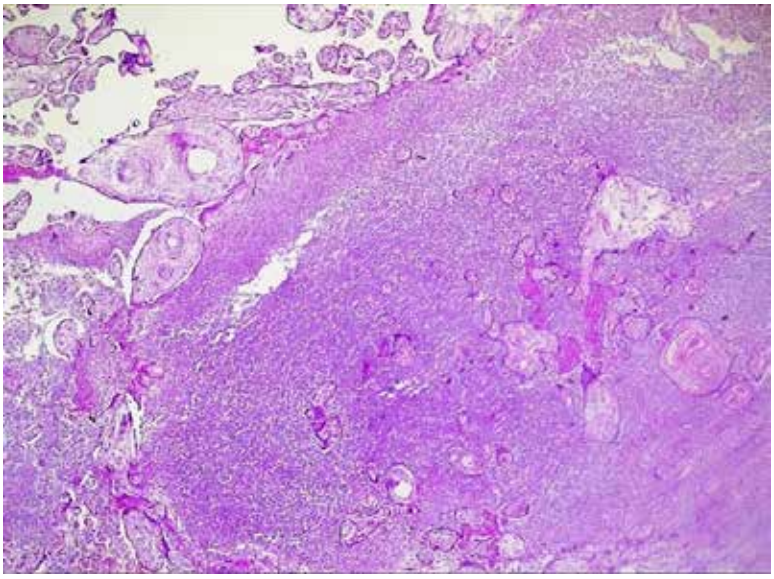

Figure 1: Histological section of placental parenchyma illustrating a destructive micro-abscess formation as a result of Listeria monocytogenes infection (courtesy of CA Wright)

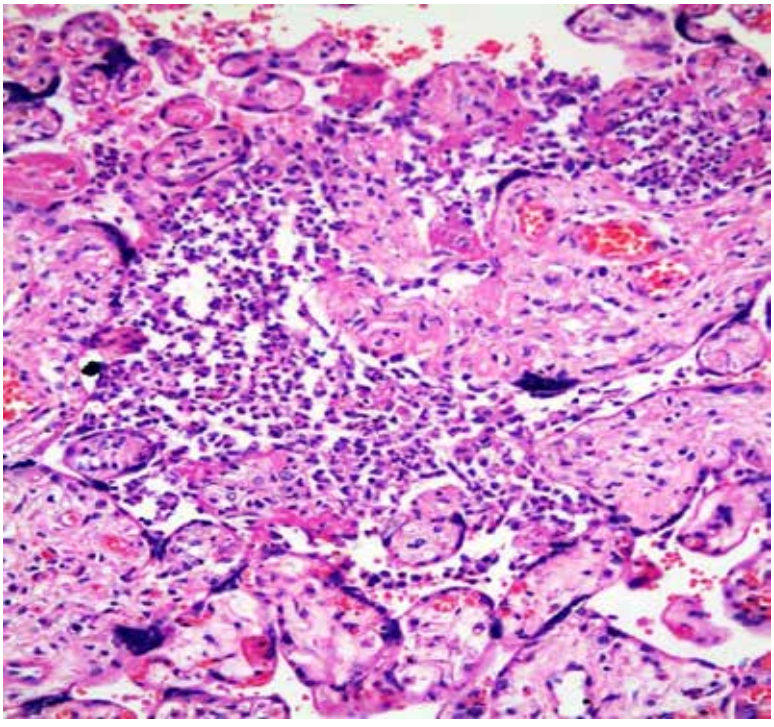

Figure 2: Placental parenchyma, chronic villitis of unknown aetiology (VUE) with villous lysis by lymphocytes. H and E stain (courtesy of CA Wright)

CA can be diagnosed both in a microbiology or histopathology laboratory and clinically.[12] However, there is a poor correlation between clinical and histologic CA. Group B *streptococcus* may show a minimal inflammatory infiltrate but causes perinatal asphyxia and leukomalacia through exotoxin-mediated vascular smooth-muscle contraction of the vessels of the umbilical cord and chorionic plate. Conversely, some bacteria, such as *Listeria monocytogenes* (see Figure 1), may show severe histologic changes with minimal maternal symptoms and present with stillbirth or a severely affected neonate.

In histology, a grading system and a staging system are used in CA where stages 2–3 are recognised to represent a fully developed histological CA and grade 2 is used when there are sub-chorionic abscesses and confluent neutrophils – Amsterdam

classification system.[10] This has prognostic significance for the neurological outcome.

The maternal response (infiltration of the chorion or sub-chorionic fibrin or decidual post-capillary venules by neutrophils) and the foetal response (neutrophils within the walls of large veins and arteries in the umbilical cord and amnion membrane) must be graded and staged.[12]

VILLITIS

Villitis can either be due to an infective agent, usually haematogenously derived. Alternatively, it can be an immunologically mediated phenomenon in which the lymphocytes within the villi are of maternal origin, therefore representing a form of maternal foetal-allograft rejection. It may be associated with intrauterine growth retardation, preterm labour and, in its severe and high-grade form, sudden, unexpected intrauterine death. It may recur in subsequent pregnancies in approximately 30% of cases with increase in severity. Villitis of unknown aetiology (VUE) low-grade and focal may occur in approximately 5–10% of all placentas and be clinically insignificant. A distinction from infective villitis may be suggested on morphology and may require immunohistochemistry and molecular testing for specific organisms, particularly viral infections such as cytomegalovirus. Class II major histocompatibility complex molecules form as the foetal immune system responds and the detrimental effects of high-grade diffuse VUE, particularly when involving stem villous vessels (obliterative foetal vasculopathy), may result in encephalopathy, cerebral palsy or intrauterine death.[12]

PLACENTAL MICROBIOME

The microbiome refers to the genetic component of all the microbes – bacteria, fungi, protozoa and viruses – that live on and inside the human body.[14] Placental microbiomes have been shown to be altered in patients with inflammation. This was assessed in a large American study using whole-genome shotgun sequencing (WGS).[15]

The Human Microbiome project consortium found that one-third of placentas from normal and term pregnancies harboured gram-positive and gram-negative bacteria. They were found to be inside the foetally derived extravillous trophoblast cells in the decidua. In a recent study by Aagaard et al using WGS technology, it was observed that the microbiome of placentas included *Escherichia coli* (the most prevalent), *Prevotella tannerae, Bacteriodes* species, *Fusobacterium* species and *Neisseria lactamica.*[16]

In another study where six nested birth cohorts were investigated, it was shown that the placental microbiome changed during pregnancy, with and without inflammation. However, the severity of CA was influenced by bacterial metabolic processes that played a role in affecting preterm birth.[15]

HOW DOES HIV STATUS INFLUENCE CHORIOAMNIOTIS?

Human immunodeficiency virus (HIV) is an incurable virus which attacks and weakens the immune system.[17] South Africa is undergoing one of the greatest HIV epidemics in the world, with approximately 19% of the general population being affected. Mother-to-child transmission (MTCT) is the biggest cause of neonatal HIV/AIDS infection.[2] In a study performed in KwaZulu-Natal, it was found that all incident HIV-infected mothers are at 2.3 times higher risk of transmitting HIV to their children.[18] An increased incidence of CA is observed in women with AIDS. It has also been reported that women with CA have an increased risk for vertical and perinatal transmission of HIV/AIDS from mother to child.[19] However, a United States study showed that the incidence of CA was similar in women with and without AIDS.[19] More of these studies are currently lacking in HIV-infected women, throughout South Africa.

PRETERM BIRTH AND IMMUNITY

The function of the neonatal immune system is compromised after intrauterine inflammation, which leads to preterm birth in most cases. Innate and adaptive immunity is immature and functions sub-optimally, and this can lead to lifelong morbidity. Owing to decreased lung function, preterm babies may require ventilation, which has adverse effects on neonatal immunity. Further, systemic inflammation (outlined earlier) is observed; this increases cytokine production, which can lead to chronic lung diseases.[20] There is decreased functionality of regulatory T cells (an important component of immune activation) in cases with with CA, and inflammation of the neonate is observed.[21]

CAESAREAN SECTION AND IMMUNITY

The gastrointestinal microbiome of infants seems to be influenced by mode of delivery –Caesarean sections versus vaginal births – at least in the very early neonatal period. The infants delivered vaginally had an increased colonisation of gut bacteria compared to those infants delivered by Caesarean section at three days old. This has been postulated to diversely affect the development and function of the neonate immune system. In addition, the absence of labour causes a reduction in monocyte expression (TLR-2 and TLR-4), which changes the neonate's response to an infectious agent.[20] The results of a study conducted in Denmark over a 14-year period showed that Caesarean section deliveries predisposed neonates to diseases associated with the mucosal immune system. These diseases included asthma, laryngitis, gastroenteritis, ulcerative colitis, celiac disease, lower respiratory tract infection and juvenile idiopathic arthritis.[22]

The colonising bacteria in the foetus obtained from the maternal gut via the placenta continue to colonise in the newborn's intestine after birth, and this significantly improves immune development and protects the newborn from various diseases. During a Caesarean section, however, the colonisation process is disrupted, and this predisposes babies to a higher incidence of allergies, type 1 diabetes and obesity.[4]

CONCLUSION

A review of the placenta highlights the important interface and function between mother and foetus. Clinicians are encouraged to review placental examinations in order to understand the prevalence and cause of infection or immune response. Elucidating the high infant mortality rate is the first step towards achieving this millennial goal.[23] A review of the placenta can assist in characterising the microbiome present in the newborn's gut passed on from the mother and in understanding further the neonatal immune system and a newborn's predisposition to certain diseases.[4]

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest

This article has been peer reviewed.

REFERENCES

1. Spong, CY, ed. Stillbirth Prediction, Prevention and Management. 2011, Blackwell Publishing Ltd.
2. Mid-year population estimates 2018. https://www.statssa.gov.za/publications/P0302/P03022018.pdf.
3. PrabhuDas M, Adkins B, Gans H, King C, et al. Challenges in infant immunity: implications for responses to infection and vaccines. Nat Immunol 2011;12(3):189– 194.
4. Walker WA. Bacterial colonization of the newborn gut, immune development, and prevention of disease. Nestle Nutr Inst Workshop Ser 2017;88:23–33.
5. Kraus FT. Placental pathology. American Registry of Pathology; 2004.
6. Gude NM, Roberts CT, Kalionis B, King RG. Growth and function of the normal human placenta. Thromb Res 2004;114(5):397–407.
7. Simpson ER, MacDonald PC. Endocrine physiology of the placenta. Ann Rev Physiol 1981;43(1):163–188.
8. Redline RW. Placental inflammation. Seminars in Fetal & Neonatal 2004;9(4):265–274.
9. Galinsky R, Polglase GR, Hooper SB, Black MJ, Moss TJ. The consequences of chorioamnionitis: Preterm birth and effects on development. J Pregnancy 2013;2013:412831.
10. Kim CJ, Romero R, Chaemsaithong P, Kim JS. Chronic inflammation of the placenta: definition, classification, pathogenesis, and clinical significance. Am J Obstet Gynecol 2015;213(4 Suppl):S53–S69.
11. Katzman PJ. Chronic inflammatory lesions of the placenta. Semin Perinatol 2015;39(1):20–26.
12. Redline RW. Villitis of unknown etiology: Noninfectious chronic villitis in the placenta. Hum Pathol 2007;38(10):1439–1446.
13. Prince AL, Ma J, Kannan PS, Alvarez M, et al. The placental membrane microbiome is altered among subjects with spontaneous preterm birth with and without chorioamnionitis. Am J Obstet Gynecol 2016;214(5):627.e1–627.e16.
14. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggitt CM, et al. The human microbiome project. Nature 2007;449:804–810.
15. Prince AL, Ma J, Kannan PS, Alvarez M, et al. The placental membrane microbiome is altered among subjects with spontaneous preterm birth with and without chorioamnionitis. Am J Obstet Gynecol 2016;214(5):627.e1–627.e16.
16. Cao B, Stout MJ, Lee I, Mysorekar IU. Placental microbiome and its role in preterm birth. Neoreviews 2014;15(12):e537–e545.
17. Stevens LM, Lynm C, Glass, RM. HIV Infection: The Basic. JAMA 2006;296(7):892–892.
18. Moodley D, Esterhuizen T, Reddy L, Moodley P, et al. Incident HIV infection in pregnant and lactating women and its effect on mother-to-child transmission in South Africa. J Infect Dis 2011;203(9):1231–1234.
19. Ocheke AN, Agaba PA, Imade GE, Silas OA, et al. Chorioamnionitis in pregnancy: A comparative study of HIV-positive and HIV-negative parturients. Int J STD AIDS 2016;27(4):296–304.
20. Melville JM, Moss TJ. The immune consequences of preterm birth. Front Neurosci 2013;7:79.
21. Rueda CM, Wells CB, Gisslen T, Jobe AH, et al. Effect of chorioamnionitis on regulatory T cells in moderate/late preterm neonates. Hum Immunol 2015;76(1):65–73.
22. Kristensen K, Henriksen L. Cesarean section and disease associated with immune function. J Allergy Clin Immunol 2016;137(2):587–590.
23. Roescher AM, Timmer A, Erwich JJ, Bos AF. Placental pathology, perinatal death, neonatal outcome, and neurological development: A systematic review. PLoS One 2014;9(2):e89419.