Review

Neonatal Immune Incompatibilities between Newborn and Mother

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Abstract: Background: Incompatibilities between the mother and unborn baby can cause complications that must be identified early to initiate the appropriate treatment. For example, neonatal alloimmune thrombocytopenia (NAIT), neonatal alloimmune neutropenia (NAIN), and morbus hemolyticus neonatorum affect children worldwide. Aim: This literature review aims to depict the similarities and differences between these three disorders from a clinical and mechanistic point of view. Material and Methods: The current literature review entailed conducting a systematic search to locate articles on the three conditions. Different electronic databases, including PsycINFO, PubMed, Web of Science, and CINAHL, were searched using the search terms “neonatal alloimmune thrombocytopenia”, “neonatal alloimmune neutropenia”, “morbus hemolyticus neonatorum”, “NAIT”, “FNAIT”, “fetal”, “NAIN”, and “hemolytic disease of the newborn”. Results: This review shows that these three diseases are caused by incompatibilities between the maternal and fetal immune systems. Furthermore, these conditions can lead to severe complications that hinder fetal development and cause death if not well managed. Discussion: The current literature review shows that NAIT, NAIN, and morbus hemolyticus neonatorum are rare conditions that occur when the mother produces antibodies against the fetal immune system. Thus, there is a need for the early detection of these conditions to initiate appropriate treatment before the child experiences adverse effects. Conclusion: The development of NAIT, NAIN, and morbus hemolyticus neonatorum is linked to the production of antibodies against the fetal immune system and fetal antigens. Further studies are required to determine potential interventions to reduce the risk of developing these three conditions.

Keywords: neonatal alloimmune thrombocytopenia (NAIT); neonatal alloimmune neutropenia (NAIN); morbus hemolyticus neonatorum

1. Introduction

The focus of this literature review is antibody-mediated diseases that arise from incompatibilities between the mother and the unborn child. Maternal antibodies produced in the blood cross the placenta to the baby and cause problems in the fetal blood such as thrombocytopenia, neutropenia, and/or the lysis of erythrocytes. Neonatal alloimmune thrombocytopenia (NAIT) is a disorder linked to maternal antibodies and immune incompatibility between the unborn baby and the mother [1]. NAIT arises when maternal antibodies act against fetal platelet alloantigens [2,3]. Although most NAIT cases tend to be mild, this disorder can cause mortality and morbidity in newborns if not detected and managed in a timely and appropriate manner [2–4]. Another disorder that has been associated with an incompatibility between the unborn baby and the maternal immune system is neonatal alloimmune
neutropenia (NAIN) [5–8], which has been associated with antagonism involving the neutrophils [6–8]. Recent investigations have reported that approximately 0.35–1.1% of NAIN cases are characterized by granulocyte-specific antibodies [7]. Finally, newborns can develop morbus hemolyticus neonatorum as a result of immune system incompatibility regarding the erythrocytes (blood type) [9–11]. The aim of this systematic review is to compare these three conditions and to depict the similarities and differences between these three disorders from a clinical and mechanistic point of view. So far, there is no review comparing all three conditions.

2. Methodology

The process entailed analyzing the results of investigations related to the topic of interest published in PsycINFO, PubMed, Web of Science, and CINAHL. The search terms and phrases were “neonatal alloimmune thrombocytopenia”, “neonatal alloimmune neutropenia”, “morbus hemolyticus neonatorum”, “NAIT”, “FNAIT”, “fetal”, “NAIN”, and “hemolytic disease of the newborn”, and Boolean operators (AND/OR) were used to combine search terms to identify additional sources for the systematic review. The search was limited to articles published in the four electronic databases between 2009 and 2019. The abstracts of the available articles were carefully reviewed to determine their quality and appropriateness (Figure 1). The initial search yielded approximately 301 articles. Other parameters, including the study type, publication year, text options, search field tags, and language, were used to limit the search. When these parameters were applied, 129 articles were obtained from the database searches, and 15 were identified by cross-referencing. The articles were carefully examined in the different stages shown in Figure 1 to determine their suitability for this review.

At the end of the search and review process, the final list of articles consisted of prospective clinical trials, experimental studies, and clinical reviews. A total of 74 studies met the inclusion criteria and were considered for review. These articles provide vital insights into the development and progression of NAIT, NAIN, and morbus hemolyticus neonatorum. Table 1 shows a summary of the 23 most important papers that were selected and reviewed in this paper.
Table 1. Summary of the 23 most important studies.

| Author                                      | Design                                                                 | Findings                                                                                                                                                                                                 |
|---------------------------------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Peterson et al. (2013) [1]                  | Review                                                                 | The authors opined that different kinds of the first human platelet antigen (HPA) have been linked to the pathogenesis of NAIT. The identification of the HPAs that increase the risk of developing the disease provides an avenue through which the disease can be diagnosed and managed. |
| Ahlen et al. (2012) [2]                     | Correlational study                                                  | The researchers reported that there was a significant link between the risk of NAIT due to anti-HPA-1a antibodies and the maternal blood type. The risk of NAIT was high among pregnant women with blood type A. |
| Arinsburg, Shaz, Westhoff, and Cushing (2012) [3] | Review                                                              | The study showed that NAIT was a major cause of intracranial hemorrhage and severe cases of thrombocytopenia. The disorder can be detected through the use of the HPA-specific antibodies and platelet genotyping with the sequence-specific primer-polymerase chain reaction (PCR-SSP) approach. |
| Bakchoul et al. (2011) [4]                  | Retrospective cohort analysis and a NOD/SCID mouse model of alloimmune thrombocytopenia | Low-avidity HPA-1a antibodies are present in a significant number of NAIT cases and, although they can escape detection by standard serology, they harbor the capability of PLT destruction in mice. |
| Porcelijn and de Haas (2018) [8]            | Review                                                                | A review of prospective screening studies showed that granulocyte-specific antibodies that caused NAIN were present in approximately 0.35–1.1% of the maternal samples. Furthermore, the researchers stated that the incidence of the disease was below 0.1%. |
| Tomicic et al. (2014) [10]                  | Prospective study                                                    | The researchers detected anti-HNA antibodies in approximately 54% of the samples that were proven to be serologically positive for alloimmune neonatal neutropenia (ANN) between 1998 and 2008. |
| Bussel and Sola-Visner (2009) [12]          | Review                                                                | The researchers stated that if a mother gives birth to a child with alloimmune thrombocytopenia, there are high chances that the next child will also develop severe NAIT. |
| Espinoza, Caradeux, Norwitz, and Illanes (2013) [13] | Review                                                              | FNAIT is a rare fetal complication that develops when a woman is alloimmunized against the platelet antigens in the fetus. |
| Tiller et al. (2016) [14]                   | Prospective observational study                                       | The authors found that there was an increase in the neonatal platelet count in HPA-1a immunized women during their subsequent pregnancies. |
| Peterson et al. (2012) [15]                 | Observational study                                                  | The study showed that HPA-2Ibw and HPA-4b were common triggers of NAIT among Caucasian women. The production of maternal antibodies against these antigens can lead to the development of NAIT. |
| Kapur et al. (2014) [16]                    | Human patient study ($n = 48$)                                        | The study showed markedly decreased levels of the fucosylation of the anti-HPA-1a specific IgG1 in FNAIT patients. Antibodies with a low amount of Fc fucose showed enhanced phagocytosis of platelets. A positive correlation of anti-HPA-1fucosylation with neonatal platelet counts was found as well as a negative correlation of anti-HPA-1fucosylation with the clinical disease severity. |
| Bakchoul et al. (2013) [17]                 | Mice study and human cell study                                       | In FNAIT, platelet destruction is mediated via the Fc part of the anti-HPA alloantibodies. Deglycosylation of antibodies abrogates the Fc-related effector functions. Deglycosylation of SZ21 abrogates Fc-effector functions without interfering with placental transport or the ability to block anti-HPA-1a binding. A therapeutical use of such an antibody might be possible. |
Table 1. Cont.

| Author                     | Design                                      | Findings                                                                                                                                                                                                 |
|----------------------------|---------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Santoso et al. (2016) [18] | Human patient study (n = 36)                 | Antibodies from mothers with ICH-positive FNAIT and with ICH-negative FNAIT were investigated and compared. The authors found a stronger binding of +ICH antibodies to endothelial cell-derived αvβ3. By absorption experiments, anti-HPA-1a antibodies with anti-αvβ3 specificity were found in the ICH positive, but not in the ICH negative cohort. Only the anti-αvβ3 subtype, but not the anti-β3 subtype was found to be able to induce epithelial cell apoptosis of HPA-1a positive epithelial cells. The maternal anti-HPA-1a subtype seems to determine the risk for ICH development of the child. |
| Winkelhorst, Oepkes, and Lopriore (2017) [19] | Review                                      | The researchers stated that the optimal intervention for the management of FNAIT was noninvasive treatment involving the weekly intravenous administration of immunoglobulin. A dose of 0.5 or 1.0 g/kg should be given to prevent aggravation of the condition. |
| Chaudhuri et al. (2012) [20] | Randomized controlled trial                 | Chaudhuri et al. (2012) concluded that the mortality factor in the granulocyte colony-stimulating factor (GCF) group was significantly lower than the rate in the control group (10% vs. 35%). |
| Ailas et al. (2015) [21]   | Randomized case-controlled study            | The study revealed that treatment with recombinant human granulocyte colony-stimulating factor therapy resulted in rapid recovery from sepsis among neutropenic children. |
| Curtis et al. (2016) [22]  | Case study                                  | The sera analysis led to the detection of IgG antibodies in women with HNA-4b+ neutrophils.                                                                                                               |
| Regan et al. (2019) [23]   | Review                                      | NAIT occurs when the immune system of the mother fails to recognize the baby’s HPAs inherited from the father. In such instances, the mother develops antibodies that can cross the placenta and attack the fetal HPAs. |
| Del Vecchio and Christensen (2012) [24] | Review                                    | The researchers opined that the early onset of neutropenia in infants was linked to cases of severe sepsis, asphyxia, periventricular hemorrhage, and maternal hypertension. |
| Basu, Kaur, and Kaur (2012) [25] | Review                                   | The scholars found out that hemolytic disease occurs as a result of Rhesus incompatibility between the mother and the fetus.                                                                                   |
| Arora et al. (2015) [26]   | Case study                                  | Morbus hemolyticus neonatorum develops due to maternal alloimmunization, a process that adversely affects the development of the fetus.                                                                       |
| Gowri et al. (2015) [27]   | Retrospective study                         | Gowri et al. stated that Rhesus incompatibility could lead to a wide range of complications such as jaundice, neonatal anemia, and respiratory distress syndrome.                                             |
| De Haas et al. (2015) [28] | Review                                      | The study showed that morbus hemolyticus neonatorum was caused by maternal alloimmunization against the fetal red blood cell antigens. The disorder could lead to anemia, icterus, and fetal death. |
3. Results

From the data collected, it is evident that incompatibility between the fetal and maternal immune systems can cause severe complications that hinder normal development and even lead to death [8,9]. Live-born affected children may experience developmental challenges and other complications that may adversely affect their chance of survival [10,11,29]. Consequently, studies are underway to ascertain the pathogenesis of these disorders and to identify management strategies. Furthermore, this review revealed that NAIT, NAIN, and morbus hemolyticus neonatorum are similar in terms of development, as they involve maternal antibodies against antigens on fetal red blood cells. A clear understanding of these disorders, however, can be more readily attained when they are individually analyzed in terms of mechanism and relevant molecules.

3.1. Neonatal Alloimmune Thrombocytopenia (NAIT) and Fetal Neonatal Alloimmune Thrombocytopenia (FNAIT)

NAIT and FNAIT are the most common reason for intracranial hemorrhage in full-term newborns [3]. Research shows that NAIT is also the leading cause of thrombocytopenia in neonates and fetuses [3,4]. Infants with severe NAIT show a wide range of symptoms, including low platelet count, florid petechial bleeding, and purpura [5]. Thrombocytopenia can occur in the absence of intravascular coagulation challenges, bacterial infection, viral infection, and other congenital disorders. Evidence from prospective and longitudinal studies has revealed that the severity of thrombocytopenia in infants at risk of developing NAIT may vary among cases [2,6]. However, it has been reported that NAIT is more common among children born to mothers with blood group A than among those born to mothers with blood group O [1]. However, further investigations are required to examine the risk of developing NAIT and its underlying pathogenesis.

There is consensus among researchers that NAIT is an immunological condition that occurs when the mother produces antibody-linked and antibody-mediated responses against the platelet-specific antigens in the fetal blood circulatory system [12]. NAIT develops when the mother lacks the specific antigen against which the immunological attack is directed. The risk of developing NAIT varies among ethnic groups. In the Caucasian community, the most immunodominant antigen is HPA-1a, which is responsible for approximately 85% of NAIT cases. Furthermore, 10% of NAIT cases have been linked to HPA-5b [1]. Irrespective of the actual cause, individuals who develop NAIT commonly experience intracranial hemorrhage, a condition that may lead to lifelong disability or death if not well managed. Intracranial hemorrhage may start at the end of the second trimester [30,31]. Without proper screening, intracranial hemorrhage may not be detected until the child is born. Consequently, poor antenatal care and management during pregnancy are considered risk factors that may increase the severity of NAIT.

In the last decade, there have been attempts to identify the antigens that are potentially associated with the pathogenesis of NAIT [1,31,32]. The antigens that cause NAIT are normally found on platelet membrane glycoproteins (GPs), such as the von Willebrand factor receptor, αIIb/β3 integrin, fibrinogen receptor, and a glycosylphosphatidylinositol (GPI)-anchored protein [1,32]. GPs usually interact with extracellular matrix proteins and coagulation factors in the cellular environment. In the long run, these interactions facilitate hemostasis [32,33]. Recent investigations have revealed that single amino acid substitutions in GPs can lead to maternal immunization during different stages of pregnancy [13,34,35]; these changes eventually lead to NAIT and affect normal development. The commonly identified GPs include CD109, GPIIIa, GPIIb, GPIbα, GPIa, and GPIbβ [1].

One common antigen class related to NAIT development that has been extensively evaluated in previous studies is the human platelet-specific antigen (HPA) class [36–38]. HPAs are platelet GP polymorphisms that can cause the production of maternal alloantibodies that attack fetal antigens [38–40]. Previous studies have shown that HPA-1a, which results from a proline/leucine substitution in the plexin–semaphorin–integrin domain of GPIIb/IIIa, can increase the risk of NAIT [41,42]. Animal model studies have revealed that fetal–maternal incompatibility for HPA-1a is the most common cause of NAIT among African and Caucasian people [43–45]. Only 2% of women are
HPA-1a negative, but this places them at risk of developing antibodies linked to HPA-1a specificity [1]. Most cases involving HPA-1a antibodies are associated with women who are positive for the class II histocompatibility antigen DRB3*0101 (DR52a) [14,46]. This correlation is further related to the fact that these women express a Leu33-containing GPIIIa peptide with a high affinity for DRB3*0101. However, further studies are required to characterize HPA-1a and analyze the possible mechanisms through which it increases the risk of NAIT.

Recent studies have shown that approximately 95% of confirmed NAIT cases among Caucasian patients are caused by maternal immunization against HPA-1, -2, -3, -5, and -15 [47,48]. However, other studies of cases negative for common HPAs have identified other mutations that encode rare HPAs [1,46,48]. Moreover, 20 of these mutations have been identified and used as the basis for explaining the development and risk of NAIT [1]. Some of the mutations that have been explored in previous studies and used to examine the immunogenic elements of NAIT include HPA-4b, HPA-6b, HPA-10b, HPA-13b, and HPA-21b [15]. While it is anticipated that additional low-frequency HPAs associated with NAIT may be identified in the future, maternal sensitization to these HPAs will account for a limited number of NAIT cases in different populations.

Researchers have also discovered that the risk and pathogenesis of NAIT are related to ABO antigens. Research has shown that some people with blood group A or B tend to have platelets that carry antigens that may be incompatible with maternal antigens [1,7], and these people have high levels of platelet A1 and B antigens [1]. These findings have raised the possibility that children with Type II high-expressor traits are at high risk of developing NAIT. However, further research is needed to determine the circumstances under which ABO antigens increase the risk of NAIT.

3.2. Modified Anti-HPA-1 Antibodies in Fetal Neonatal Alloimmune Thrombocytopenia (FNAIT)

Kapur et al. have demonstrated in 2014 that a prominent lack of IgG-fucosylation of anti-HPA-1a antibodies is present in sera of FNAIT patients [16]. This lack of fucosylation causes an enhancement of the antibody-mediated phagocytosis of platelets through increased binding of the antibodies on platelets to FcgRIIIa/b. Thereby the degree of anti-HPA-1a fucosylation positively correlates with the neonatal platelet counts in FNAIT and negatively correlates to the clinical disease severity.

Analogously Bakchoul et al. have demonstrated the importance of a deglycosylated monoclonal anti-HPA-1a antibody from a therapeutic point of view in a mouse model [17]. Deglycosylation of antibodies abrogates the Fc-related effector functions. Therefore an Fc inactive deglycosylated monoclonal anti-HPA-1a antibody could potentially serve as a therapeutic tool in FNAIT in the near future by competitively inhibiting the binding of maternal alloantibodies [17].

Furthermore, in FNAIT neonates, the antibody titer does NOT strictly correlate with the clinical disease severity as with intracerebral hemorrhages. Intracerebral hemorrhage, thereby, is the most feared complication of FNAIT neonates. Thus other factors are likely involved in this respect, such as the IgG-FC-glycosylation patterns and other factors, as discussed by Sachs and Santoso in 2017 [49]. In addition, the role of anti-endothelial antibodies as a cause of intracerebral hemorrhage in FNAIT has been discussed by Santoso et al. in 2016 [18].

3.3. Neonatal Alloimmune Neutropenia

In some cases, incapability between the maternal and fetal immune systems results in NAIN. Although this condition is rare, it can adversely affect fetal development and lead to death [7]. The main signs of NAIN include pneumonia, meningitis, sepsis, and omphalitis. Furthermore, NAIN can lead to skin infections. Interestingly, NIAN is linked to cases in which the mother develops alloantibodies against the neutrophil antigens inherited by the fetus from the father [8,9]. Like other autoimmune disorders, NAIN has a complex pathogenesis and underlying mechanism of development [19,51,52]. Thus, there are continued research and clinical development efforts to gather additional information on NAIN [53–55]. There is consensus among researchers that
NAIN usually occurs when maternal antibodies are sensitized to fetal neutrophils in the fetus [56–59]. Antibodies in the immunoglobulin G (IgG) class are transported across the placenta. Once these antibodies reach the fetus, they act on fetal neutrophils, causing cellular destruction [20,60,61]. Furthermore, these antibodies can inhibit granulopoiesis. In certain instances, NAIN is linked to isoantibodies such as HNA-2 and/or other HNA antibodies.

Researchers have identified different classes of human neutrophil antigen (HNA) associated with the development of NAIN [21,22,62]. Currently, a total of 11 HNAs grouped into five HNA classes, HNA-1, HNA-2, HNA-3, HNA-4, and HNA-5, have been identified in previous studies and linked to NAIN development. The HNA-1 group is usually carried through Fc gamma receptor IIIb (FcγRIIIb) [63,64].

In this class, four primary HNAs have been associated with the development of NAIN, including HNA-1a, b, c, and d. A combination of these HNAs has been observed in patients with NAIN.

The second class is the HNA-2 group that contains two variants, the HNA-2-positive and CD177 (HNA-2)-negative neutrophil groups [23,24,65,66].

The third category is the HNA-3 system, which consists of two antigens, HNA-3a and HNA-3b. In other cases, the development of NAIN is linked to the HNA-4 system, which consists of the HNA-4a and HNA-4b alleles. Finally, the HNA-5 system contains a single antigen, HNA-5a, that has also been implicated in NAIN development [67,68]. A review of previous studies shows that any HNA group can increase the risk of NAIN [69]. However, only a few cases of NAIN have been linked to the production of HNA-3a, HNA-3b, HNA-4b, and HNA-5a. Antibodies against these neutrophils can be detected through the leucoagglutination technique. In other studies, researchers used monoclonal antibody immobilization of granulocyte antigens (MAIGA) and the granulocyte immunofluorescence test (GIFT) to identify maternal antibodies that potentially attack fetal HNAs and lead to the development of NAIN [7].

3.4. Morbus Hemolyticus Neonatorum

Morbus hemolyticus neonatorum is an alloimmune condition that occurs when maternal IgG attacks antigens on fetal red blood cells. Notably, IgG is one of the main antibodies produced by the mother [25,26], and it can target antigens in the fetal circulation in cases of complete incompatibility [25–28]. In such cases, IgG breaks down and destroys the antigens on fetal red blood cells through hemolysis. Over time, the fetus commonly develops anemia or reticulocytosis [30]. The severity of the disorder may vary among cases [27,28], and this disorder can lead to complications such as heart failure or even death. Morbus hemolyticus neonatorum, similar to NAIT and NIAN, is a disorder associated with immune system incompatibility or impairment that affects immune tolerance during pregnancy [26,28]. Thus, these conditions can adversely impact fetal development and lead to severe complications or even death [26].

Research evidence shows that morbus hemolyticus neonatorum is primarily caused by Rhesus incompatibility between the mother and child [25,26,70,71]. In some cases, however, this disorder has been associated with both Rhesus incompatibility and fetal alloimmune thrombocytopenia [25,26,72]. In such instances, the child may show low fetal hemoglobin and platelet levels. It is imperative that treatment is initiated early to ensure the survival of the child; treatment may entail the transfusion of packed red cells and platelets through the umbilical vein.

3.5. Therapeutic Strategies

NAIT, NAIN, and morbus hemolyticus neonatorum can adversely affect the wellbeing of infants. Thus, research is underway to explore interventions for disease management [7]. For NAIT, the standard intervention is intravenous human immunoglobulin (IVIG) administration, which aims to increase fetal platelet count [46]. However, the actual mechanism through which IVIG alleviates NAIT is not yet fully understood. NAIN, on the other hand, is managed by prophylactic treatment and granulocyte-colony stimulating factor (G-CSF) [56,59].
For NAIT / FNAIT patients, IVIg is only administered in second and subsequent pregnancies, so far we do not have a reliable test to predict clinical disease severity of NAIT in first pregnancies.

The administration of G-CSF can increase the neutrophil population, thus improving the survival rate of affected children [60]. Finally, morbus hemolyticus neonatorum can be managed through increased fluid intake, light therapy, and IVIg administration to protect the child’s red blood cells from destruction [71–73]. In other cases, researchers have suggested that exchange transfusion can be used to manage morbus hemolyticus neonatorum [74]. However, further investigations are needed to gather additional information on the efficacy of various interventions.

4. Discussion

NAIT, NAIN, and morbus hemolyticus are conditions that may affect normal fetal development [1,15,26,73]. The main similarity among these conditions is that they are caused by incompatibilities between the mother and the unborn child (Table 2). NAIT occurs due to the passive transfusion of maternal antibodies that eventually target platelet antigens [74], and NAIN arises when maternal anti-neutrophil antibodies become sensitized to fetal neutrophils, which leads to the destruction of these cells. Cases of both conditions are rare in part because only a few HLA antibodies can cause NAIT. The current review reveals that NAIT is considered the platelet analog of the Rhesus incompatibility that causes morbus hemolyticus neonatorum.

Table 2. Summary of the major findings.

| Platelet-Specific Antigens Associated with NAIT | Neutrophil Antigens Associated with NAIN | Risk Factor for Morbus Hemolyticus Neonatorum |
|-----------------------------------------------|----------------------------------------|-----------------------------------------------|
| HPA-1a [1,2]                                  | HNA-1a, b, c, and d [7]                | Rhesus incompatibility [67,68]                 |
| HPA-2b [1]                                    | HNA-2 positive and                     |                                               |
| HPA-3a [3,4]                                  | HNA-2-negative (CD177) [19,52]        |                                               |
| HPA-3b [3,4]                                  | HNA-3a and HNA-3b [7]                 |                                               |
| HPA-4b [5,6]                                  | HNA-4a and HNA-4b [53–55]             |                                               |
| HPA-5a [1]                                    | HNA-5a [54,56]                         |                                               |
| HPA-6b [8]                                    |                                        |                                               |
| HPA-10b [10]                                  |                                        |                                               |
| HPA-13b [30]                                  |                                        |                                               |
| HPA-15 [32]                                   |                                        |                                               |
| HPA-16 [15,32]                                |                                        |                                               |
| HPA-21b [1]                                   |                                        |                                               |

Thus, there is a need to carefully screen the fetus in the early stages of the pregnancy to determine the possible risks of NAIT, NAIN, and morbus hemolyticus.

5. Conclusions

Different conditions occur during pregnancy and may affect the normal development of the fetus. In some cases, the antibody-mediated diseases arising from incompatibilities between the mother and the unborn child may lead to complications during and after pregnancy. NAIT, NAIN, and morbus hemolyticus are examples of the diseases that occur due to maternal and fetal incompatibilities. While the disorders are considered to be antibody-mediated diseases, the actual causes differ in each case. Thus, expectant mothers should be carefully screened to determine the presence of antibodies that may lead to the occurrence of NAIT, NAIN, and morbus hemolyticus. Further studies are also required to identify new interventions that can help reduce the risk of these three conditions and prevent adverse effects.

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References

1. Peterson, J.A.; McFarland, J.G.; Curtis, B.R.; Aster, R.H. Neonatal alloimmune thrombocytopenia: Pathogenesis, diagnosis and management. Br. J. Haematol. 2013, 161, 3–14. [CrossRef] [PubMed]

2. Ahlen, M.T.; Husebekk, A.; Killie, M.K.; Kjeldsen-Kragh, J.; Olsson, M.L.; Skogen, B. The development of severe neonatal alloimmune thrombocytopenia due to anti-HPA-1a antibodies is correlated to maternal ABO genotypes. Clin. Dev. Immunol. 2012, 2012, 156867. [CrossRef] [PubMed]

3. Arinsburg, S.A.; Shaz, B.H.; Westhoff, C.; Cushing, M.M. Determination of human platelet antigen typing by molecular methods: Importance in diagnosis and early treatment of neonatal alloimmune thrombocytopenia. Am. J. Hematol. 2012, 87, 525–528. [CrossRef] [PubMed]

4. Bakchoul, T.; Kubiak, S.; Krautwurst, A.; Roderfeld, M.; Siebert, H.C.; Bux, J.; Sachs, U.J.; Santoso, S. Low-avidity anti-HPA-1a alloantibodies are capable of antigen-positive platelet destruction in the NOD/SCID mouse model of alloimmune thrombocytopenia. Transfusion 2011, 51, 2455–2461. [CrossRef]

5. Bessos, H.; Killie, M.K.; Seghatchian, J.; Skogen, B.; Urbaniak, S.J. The relationship of anti-HPA-1a amount to severity of neonatal alloimmune thrombocytopenia—Where does it stand? Transfus. Apher. Sci. 2009, 40, 75–78. [CrossRef]

6. Bussel, J. Diagnosis and management of the fetus and neonate with alloimmune thrombocytopenia. J. Thromb. Haemost. 2009, 7 (Suppl. 1), 253–257. [CrossRef]

7. Van den Tooren-de Groot, R.; Ottink, M.; Huiskes, E.; van Rossum, A.; van der Voorn, B.; Slomp, J.; de Haas, M.; Porcelijn, L. Management and outcome of 35 cases with fetal/neonatal alloimmune neutropenia. Acta Paediatr. 2014, 103, e467–e474. [CrossRef]

8. Porcelijn, L.; de Haas, M. Neonatal alloimmune neutropenia. Transfus. Med. Hemother. 2018, 45, 311–316. [CrossRef]

9. Kissel, K.; Santoso, S.; Hofmann, C.; Stroncek, D.; Bux, J. Molecular basis of the neutrophil glycoprotein NB1 (CD177) involved in the pathogenesis of immune neutropenias and transfusion reactions. Eur. J Immunol. 2001, 31, 1301–1309. [CrossRef]

10. Tomicic, M.; Starcevic, M.; Ribicic, R.; Golubic-Cepulic, B.; Hundric-Haspl, Z.; Jukic, I. Alloimmune neonatal neutropenia in Croatia during the 1998-2008 period. Am. J. Reprod. Immunol. 2014, 71, 451–457. [CrossRef]

11. Boxer, L.A.; Bolyard, A.A.; Kelley, M.L.; Marrero, T.M.; Phan, L.; Bond, J.M.; Newburger, P.E.; Dale, D.C. Use of granulocyte colony-stimulating factor during pregnancy in women with chronic neutropenia. Obs. Gynecol. 2015, 125, 197–203. [CrossRef] [PubMed]

12. Bussel, J.B.; Sola-Vinser, M. Current approaches to the evaluation and management of the fetus and neonate with immune thrombocytopenia. Semin. Perinatol. 2009, 33, 35–42. [CrossRef] [PubMed]

13. Espinoza, J.P.; Caradeux, J.; Norwitz, E.R.; Illanes, S.E. Fetal and neonatal alloimmune thrombocytopenia. Rev. Obstet Gynecol. 2013, 6, e15–e21. [PubMed]

14. Tiller, H.; Kuster, A.; Skogen, B.; Kjeldsen-Kragh, J.; Kjaer, M. True risk of fetal/neonatal alloimmune thrombocytopenia in subsequent pregnancies: A prospective observational follow-up study. BJOG 2016, 123, 738–744. [CrossRef]

15. Kapur, R.; Kustiawan, I.; Vestrheim, M.; Kocher, M.A.; Visser, R.; Einarsson, H.K.; Porcelijn, L.; Jackson, D.; Kumpel, B.; Deelder, A.M.; et al. A prominent lack of IgG1-Fc fucosylation of platelet alloantibodies in pregnancy. Blood 2014, 123, 471–480. [CrossRef]

16. Bakchoul, T.; Greinacher, A.; Sachs, U.J.; Kräutwurst, A.; Renz, H.; Harb, H.; Bein, G.; Newman, P.J.; Santoso, S. Inhibition of HPA-1a Alloantibody-Mediated Platelet Destruction by a Deglycosylated anti-HPA-1a Monoclonal Antibody in Mice: Toward Targeted Treatment of Fetal-Autoimmune Thrombocytopenia. Blood 2013, 122, 321–327. [CrossRef]

17. Santos, S.; Wahidmadyatami, H.; Bakchoul, T.; Werth, S.; Al-Fakhri, N.; Bein, G.; Kiefel, V.; Zhu, J.; Newman, P.J.; Bayat, B.; et al. Anti-endothelial αvβ3 antibodies are a major cause of intracranial bleeding in fetal-neonatal alloimmune thrombocytopenia. Arter. Thromb. Vasc. Biol. 2016, 36, 1517–1524. [CrossRef]
19. Winkelhorst, D.; Oepkes, D.; Lopriore, E. Fetal and neonatal alloimmune thrombocytopenia: Evidence based antenatal and postnatal management strategies. *Expert Rev. Hematol.* 2017, 10, 729–737. [CrossRef]

20. Chaudhuri, J.; Mitra, S.; Mukhopadhyay, D.; Chakraborty, S.; Chatterjee, S. Granulocyte colony-stimulating factor for preterm babies with sepsis and neutropenia: A randomized controlled trial. *J. Clin. Neonatol.* 2012, 1, 202–206. [CrossRef]

21. Akta¸s, D.; Demirel, B.; Gürsoy, T.; Ovalı, F. A randomized case-controlled study of recombinant human granulocyte colony stimulating factor for the treatment of sepsis in preterm neutropenic infants. *Pediatr. Neonatol.* 2015, 56, 171–175. [CrossRef] [PubMed]

22. Curtis, B.R.; Roman, A.S.; Sullivan, M.J.; Raven, C.S.; Larison, J.; Weitekamp, L.A. Two cases of maternal alloimmunization against human neutrophil alloantigen-4b, causing severe alloimmune neonatal neutropenia. *Transfusion* 2016, 56, 101–106. [CrossRef] [PubMed]

23. Regan, F.; Lees, C.C.; Jones, B.; Nicolaides, K.H.; Wimalasundera, R.C.; Mijovic, A. Prenatal management of pregnancies at risk for fetal neonatal alloimmune thrombocytopenia (FNAIT): Scientific impact paper no. 61. *BJOG* 2019, 126, e173–e185. [CrossRef] [PubMed]

24. Del Vecchio, A.; Christensen, R.D. Neonatal neutropenia: What diagnostic evaluation is needed and when is treatment recommended? *Early Hum. Dev.* 2012, 88 (Suppl. 2), S19–S24. [CrossRef]

25. Basu, S.; Kaur, R.; Kaur, G. Hemolytic disease of the fetus and newborn: Current trends and perspectives. *Asian J. Transfus. Sci.* 2011, 5, 3–7. [CrossRef]

26. Arora, S.; Doda, V.; Maria, A.; Kotwal, U.; Goyal, S. Maternal anti-M induced hemolytic disease of newborn followed by prolonged anemia in newborn twins. *Asian J. Transfus. Sci.* 2015, 9, 98–101. [CrossRef]

27. Gowri, V.; Al-Dughaishi, T.; Al-Rubkhı, I.; Al-Duhlı, M.; Al-Harrasi, Y. Alloimmunization due to red cell antibodies in Rhesus positive Omani pregnant women: Maternal and perinatal outcome. *Asian J. Transfus. Sci.* 2015, 9, 150–154. [CrossRef]

28. De Haas, M.; Thurik, F.; Koelwijn, J.; Van Der Schoot, C. Haemolytic disease of the fetus and newborn. *Vox Sang.* 2015, 109, 99–113. [CrossRef]

29. Rath, M.E.A.; Smits-Wintjens, V.E.H.J.; Oepkes, D.; Walther, F.J.; Lopriore, E. Iron status in infants with alloimmune hemolytic disease in the first three months of life. *Vox Sang.* 2013, 105, 328–333. [CrossRef]

30. Smith, G.A.; Rankin, A.; Riddle, C.; Cheetham-Wilkinson, C.; Ranasinghe, N.; Evseiah, W.H.; Watkins, N.A. Severe Fetomaternal Alloimmune Thrombocytopenia Due to Anti-Human Platelet Antigen (HPA)-1a in a Mother With a Rare and Silenced ITGB3*0101 (GPIIIa) Allele. *Vox Sang.* 2007, 93, 325–330. [CrossRef]

31. Tiller, H.; Kamphuis, M.M.; Flodmark, O.; Papa-dogiannakis, N.; David, A.L.; Sainio, S.; Koskinen, S.; Javela, K.; Wikman, A.T.; Kekomaki, R.; et al. Fetal intracranial haemorrhages caused by fetal and neonatal alloimmune thrombocytopenia: An observational cohort study of 43 cases from an international multicentre registry. *BMJ Open* 2013, 3, e002490. [CrossRef] [PubMed]

32. Paridaans, N.P.; Kamphuis, M.M.; TauneWikman, A.; Tiblad, E.; Van den Akker, E.S.; Lopriore, E.; Challis, D.; Westgren, M.; Oepkes, D. Low-dose versus standard-dose intra-venous immunoglobulin to prevent fetalintracranial hemorrhage in fetal and neonatal alloimmune thrombocytopenia: A randomized trial. *Fetal Diagn. Ther.* 2015, 38, 147–153. [CrossRef] [PubMed]

33. Kjaer, M.; Bertrand, G.; Bachhouli, T.; Massey, E.; Baker, J.M.; Lieberman, L.; Tanael, S.; Greinacher, A.; Murphy, M.F.; Arnold, D.M.; et al. Maternal HPA-1a antibody level and its role in predicting the severity of Fetal/Neonatal Alloimmune Thrombocytopenia: A systematic review. *Vox Sang.* 2019, 114, 79–94. [CrossRef] [PubMed]

34. Reeves, H.M. Immune-mediated cytopenia in the pediatric setting, immunologic concepts in transfusion medicine. *Bone Marrow Transpl.* 2017, 52, 1571–1574.

35. Kim, C.J.; Romero, R.; Chaemsaithong, P.; Kim, J.S. Chronic inflammation of the placenta: Definition, classification, pathogenesis, and clinical significance. *Am. J. Obstet. Gynecol.* 2015, 213 (Suppl. 4), S53–S69. [CrossRef]

36. Skogen, B.; Killie, M.K.; Kjeldsen-Kragh, J. Reconsidering fetal and neonatal alloimmune thrombocytopenia with a focus on screening and prevention. *Expert Rev. Hematol.* 2010, 3, 559–566. [CrossRef]

37. Gyamfi-Bannerman, C.; Thom, E.A.; Blackwell, S.C. Antenatal betamethasone for women at risk for late preterm delivery. *N Engl J Med.* 2016, 374, 1311–1320. [CrossRef]

38. Kamphuis, M.; Paridaans, N.; Porcelijn, L. Screening in pregnancy for fetal or neonatal alloimmune thrombocytopenia: Systematic review. *BJOG* 2010, 117, 1335–1343. [CrossRef]
39. Rayment, R.; Brunskill, S.J.; Soothill, P.W. Antenatal interventions for fetomaternal alloimmune thrombocytopenia. *Cochrane Database Syst. Rev.* 2011, 5, CD004226. [CrossRef]
40. Scheffer, P.; Ait Soussan, A.; Verhagen, O. Noninvasive fetal genotyping of human platelet antigen-1a. *BJOG* 2011, 118, 1392–1395. [CrossRef]
41. Vinograd, C.A.; Bussel, J.B. Antenatal treatment of fetal alloimmune thrombocytopenia: A current perspective. *Haematologica* 2010, 95, 1807–1811. [CrossRef] [PubMed]
42. Knight, M.; Pierce, M.; Allen, D.; Kurinczuk, J.J.; Spark, P.; Roberts, D.J.; Murphy, M.F. The incidence and outcomes of fetomaternal alloimmune thrombocytopenia: A UK national study using three data sources. *Br. J. Haematol.* 2011, 152, 460–468. [CrossRef] [ PubMed]
43. Bussel, J.B.; Berkowitz, R.L.; Hung, C.; Kolb, E.A.; Wissert, M.; Primiani, A.; Tsaur, F.W.; McFarland, J.G. Intracranial hemorrhage in alloimmune thrombocytopenia: Stratified management to prevent recurrence in the subsequent affected fetus. *Am. J. Obstet. Gynecol.* 2010, 203, 135-e1. [CrossRef] [PubMed]
44. Provan, D.; Stasi, R.; Newland, A.C. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010, 115, 168–175. [CrossRef]
45. Wu, G.G.; Kaplan, C.; Curtis, B.R.; Pearson, H.A. Report of the 14th international society of blood transfusion platelet immunology workshop. *Vox Sang.* 2010, 99, 375–381. [CrossRef]
46. Tiller, H.; Killie, M.K.; Husebekk, A.; Skogen, B.; Ni, H.; Kjeldsen-Kragh, J.; Øian, P. Platelet antibodies and fetal growth: Maternal antibodies against fetal platelet antigen 1a are strongly associated with reduced birth weight in boys. *Acta Obs. Gynecol. Scand.* 2012, 91, 79–86. [CrossRef]
47. Ghevaert, C.; Rankin, A.; Huiskes, E.; Porcelijn, L.; Javela, K.; Kekomaki, R.; Bakchoul, T.; Santoso, S.; Pacheco, L.D.; Berkowitz, R.L.; Moise, K.J., Jr.; Bussel, J.B.; McFarland, J.G.; Saade, G.R. Fetal and neonatal alloimmune thrombocytopenia: A management algorithm based on risk stratification. *Obstet. Gynecol.* 2011, 118, 1157–1163. [CrossRef]
48. Sachs, U.J.; Santos, S. Bleeding or no bleeding? Anti-endothelial alphaVbeta3 antibodies as a major cause of intracranial haemorrhage in fetal-neonatal alloimmune thrombocytopenia. *ISBT Sci. Ser.* 2017, 13, 59–69. [CrossRef]
49. Middelburg, R.A.; Porcelijn, L.; Lardy, N.; Briët, E.; Vrielink, H. Prevalence of leucocyte antibodies in the Dutch donor population. *Vox Sang.* 2011, 100, 327–335. [CrossRef]
50. Middelburg, R.A.; Vrielink, H.; Porcelijn, L. Prevalence of granulocyte antibodies in never allo-exposed female and male donors. *Eur J. Haematol.* 2017, 98, 250–253. [CrossRef] [PubMed]
51. INIS Collaborative Group; Brocklehurst, P.; Farrell, B.; King, A.; Juszczak, E.; Darlow, B.; Haque, K.; Nutland, S.; Smyth, D.J.; et al. Alloantibodies against low-frequency human platelet antigens do not account for a significant proportion of cases of fetomaternal alloimmune thrombocytopenia: Evidence from 1054 cases. *Transfusion* 2009, 49, 2084–2089. [CrossRef]
52. Pacheco, L.D.; Berkowitz, R.L.; Moise, K.J., Jr.; Bussel, J.B.; McFarland, J.G.; Saade, G.R. Fetal and neonatal alloimmune thrombocytopenia: A management algorithm based on risk stratification. *Obstet. Gynecol.* 2011, 118, 1157–1163. [CrossRef] [PubMed]
53. Xia, W.; Simtong, P.; Santos, S. Neutrophil alloantigens and alloantibodies in different populations. *ISBT Sci. Ser.* 2017, 12, 62–67. [CrossRef]
54. Xia, W.; Ye, X.; Xu, X.; Chen, D.; Deng, J.; Chen, Y.; Ding, H.; Shao, Y.; Wang, J.; Liu, J.; et al. The prevalence of leucocyte alloantibodies in blood donors from South China. *Transfus. Med.* 2015, 25, 385–392. [CrossRef] [PubMed]
55. Desenfants, A.; Jeziorski, E.; Plan, O.; Rodière, M.; Rimbert, M.; Muller, J.Y.; Taib, J.; Cambonie, G. Intravenous immunoglobulins for neonatal alloimmune neutropenia refractory to recombinant human granulocyte colony-stimulating factor. *Am. J. Perinatol.* 2011, 28, 461–466. [CrossRef]
56. Reil, A.; Sachs, U.J.; SiahaniDou, T.; Flesch, B.K.; Bux, J. HNA-1d: A new human neutrophil antigen located on Fc-receptor IIIb associated with neonatal immune neutropenia. *Transfusion* 2013, 53, 2145–2151. [CrossRef]
57. Reil, A.; Flesch B, J.; Xie, J. FCGR3B*04—A novel allele of the human Fc gamma receptor IIIb gene. *Transfus. Med. Hemother.* 2011, 38 (Suppl. 1), 69–75. [CrossRef] [PubMed]
58. Nagelkerke, S.Q.; Tacke, C.E.; Breunis, W.B.; Geissler, J.; Sins, J.W.; Appelhof, B.; van den Berg, T.K.; de Boer, M.; Kuijpers, T.W. Nonallelic homologous recombination of the FCGR2/3 locus results in copy number variation and novel chimeric FCGR2 genes with aberrant functional expression. *Genes Immun.* 2015, 16, 422–429. [CrossRef]
59. Chiba, A.K.; Kimura, E.Y.; Albuquerque, D.; Guirão, F.P.; Yamamoto, M.; Costa, F.F.; Bordin, J.O. Molecular studies reveal that A134T, G156A and G1333A SNPs in the CD177 gene are associated with atypical expression of human neutrophil antigen-2. Vox Sang. 2010, 98, 160–166.

60. Greinacher, A.; Wesche, J.; Hammer, E.; Fürll, B.; Völker, U.; Reil, A.; Bux, J. Characterization of the human neutrophil alloantigen-3a. Nat. Med. 2010, 16, 45–48. [CrossRef]

61. Curtis, B.R.; Cox, N.J.; Sullivan, M.J.; Konkashbaev, A.; Bowens, K.; Hansen, K.; Aster, R.H. The neutrophil alloantigen HNA-3a (5b) is located on choline transporter-like protein 2 and appears to be encoded by an R>Q154 amino acid substitution. Blood 2010, 115, 2073–2076. [CrossRef] [PubMed]

62. Lopes, L.B.; Abbas, S.A.; Moritz, E.; Martins, J.O.; Chiba, A.K.; Langhi, D.M., Jr.; Bordin, J.O. Antibodies to human neutrophil antigen HNA-3b implicated in cases of neonatal alloimmune neutropenia. Transfusion 2018, 58, 1264–1270. [CrossRef] [PubMed]

63. Porcelijn, L.; Abbink, F.; Terraneo, L.; Onderwater-vd Hoogen, L.; Huiskes, E.; de Haas, M. Neonatal alloimmune neutropenia due to immunoglobulin G antibodies against human neutrophil antigen-5a. Transfusion 2011, 51, 574–577. [CrossRef] [PubMed]

64. Lee, J.A.; Sauer, B.; Tuminski, W.; Cheong, J.; Fitz-Henley, J., 2nd; Mayers, M.; Ezuma-Igwe, C.; Arnold, C.; Hornik, C.P.; Clark, R.H.; et al. Best Pharmaceuticals for Children Act—Pediatric Trials Network Steering Committee Effectiveness of granulocyte colony-stimulating factor in hospitalized infants with neutropenia. Am. J. Perinatol. 2017, 34, 458–464. [CrossRef] [PubMed]

65. Taaning, E.; Jensen, L.; Varming, K. Simultaneous Occurrence of Foetal and Neonatal Alloimmune Thrombocytopenia and Neonatal Neutropenia Due to Maternal Neutrophilic Autoantibodies: A Case Study and Review of the Literature. Acta Paediatr. 2012, 101, 896–899. [CrossRef]

66. Kikkawa, M.; Matsubara, S.; Takatoku, M.; Kuwata, T.; Ohkuchi, A.; Izumi, A.; Watanabe, T.; Suzuki, M. Granulocyte-colony Stimulating Factor for the Treatment of Ritodrine- Induced Neutropenia. J. Obstet. Gynaecol. Res. 2008, 34, 286–290. [CrossRef]

67. Maheshwari, A. Neutropenia in the newborn. Curr. Opin. Hematol. 2014, 21, 43–49. [CrossRef]

68. ISBT Working Party on Granulocyte Immunobiology; Bierling, P.; Bux, J.; Curtis, B.; Flesch, B.; Fung, L.; Lucas, G.; Macek, M.; Muniz-Diaz, E.; Porcelijn, L.; et al. Recommendations of the ISBT Working Party on Granulocyte Immunobiology for leucocyte antibody screening in the investigation and prevention of antibody-mediated transfusion-related acute lung injury. Vox Sang. 2009, 96, 266–269.

69. Wiedl, C.; Walter, A.W. Granulocyte colony stimulating factor in neonatal alloimmune neutropenia: A possible association with induced thrombocytopenia. Pediatr. Blood Cancer. 2010, 54, 1014–1046. [CrossRef]

70. Águeda, S.; Rocha, G.; Ferreira, F.; Bonito, V.; Margarida, L.; Guimarães, H. Neonatal alloimmune neutropenia: Still a diagnostic and therapeutic challenge. J. Pediatr. Hematol. 2012, 34, 497–499.

71. Giers, G.; Wenzel, F.; Stockschläder, M.; Riethmüller, R.; Lorenz, H.; Tutschek, B. Fetal alloimmune thrombocytopenia and maternal intravenous immunoglobulin infusion. Haematologica 2010, 95, 1921–1926. [CrossRef] [PubMed]

Bertrand, G.; Drame, M.; Martageix, C.; Kaplan, C. Prediction of the fetal status in noninvasive management of alloimmune thrombocytopenia. Blood 2011, 117, 3209–3213. [CrossRef] [PubMed]

Rayment, R.; Kooij, T.W.; Zhang, W.; Siebold, C.; Murphy, M.F.; Allen, D.; Wilcox, N.; Roberts, D.J. Evidence for the specificity for platelet HPA-1a alloepitope and the presenting HLA-DR52a of diverse antigen-specific helper T cell clones from alloimmunized mothers. J. Immunol. 2009, 183, 677–686. [CrossRef] [PubMed]

Sachs, U.J.; Bakchoul, T.; Eva, O.; Giptner, A.; Bein, G.; Aster, R.H.; Gitter, M.; Peterson, J.; Santos, S. A point mutation in the EGF-4 domain of beta (3) integrin is responsible for the formation of the Sec(a) platelet alloantigen and affects receptor function. Thromb. Haemost. 2012, 107, 80–87. [CrossRef]