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Fetal and neonatal alloimmune thrombocytopenia: recommendations for evidence-based practice, an international approach

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Abstract

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) may result in severe bleeding, particularly fetal and neonatal intracranial haemorrhage (ICH). As a result, FNAIT requires prompt identification and treatment; subsequent pregnancies need close surveillance and management. An international panel convened to develop evidence-based recommendations for diagnosis and management of FNAIT. A rigorous approach was used to search, review and develop recommendations from published data for: antenatal management, postnatal management, diagnostic testing and universal screening. To confirm FNAIT, fetal human platelet antigen (HPA) typing, using non-invasive methods if quality-assured, should be performed during pregnancy when the father is unknown, unavailable for testing or heterozygous for the implicated antigen. Women with a previous child with an ICH related to FNAIT should be offered intravenous immunoglobulin (IVIG) infusions during subsequent affected pregnancies as early as 12 weeks gestation. Ideally, HPA-selected platelets should be available at delivery for potentially affected infants and used to increase the neonatal platelet count as needed. If HPA-selected platelets are not immediately available, unselected platelets should be transfused. FNAIT studies that optimize antenatal and postnatal management, develop risk stratification algorithms to guide management and standardize laboratory testing to identify high risk pregnancies are needed.

Keywords: Guideline, fetal, haematology, HPA-1a.

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Fetal and neonatal alloimmune thrombocytopenia (FNAIT) occurs when maternal IgG alloantibodies to human platelet antigens (HPAs) traverse the placenta and cause fetal platelet destruction and, potentially, suppression of megakaryopoiesis (Liu *et al*, 2015). The reported incidence ranges from 0·3 to 1 in 1000 (Williamson *et al*, 1998; Turner *et al*, 2005; Kjeldsen-Kragh *et al*, 2007), and depends on how cases are accrued: screening versus clinical presentation, usually of a thrombocytopenic neonate. Presentations range from an asymptomatic neonate to neonatal thrombocytopenia, petechiae, ecchymosis and intracranial haemorrhage (ICH). FNAIT-related ICH is reported to occur in 0·02–0·1:1000 live births (Kjeldsen-Kragh *et al*, 2007; Kamphuis *et al*, 2010). When ICHs occur, they frequently occur *in utero* – 54% occur before 28 weeks gestation (Tiller *et al*, 2013). The consequences of ICH include death (35%) or serious neurological sequelae in up to 83% of survivors (Tiller *et al*, 2013). Optimal management is required to reduce or eliminate the risk of ICH in the fetus and neonate.

An international panel of adult and paediatric haematologists, maternal fetal medicine specialists, paediatricians, methodologists, transfusion medicine physicians and a patient representative was convened by the International Collaboration for Transfusion Medicine Guidelines (ICTMG) to provide guidance on the antenatal and postnatal management of FNAIT for haematologists, maternal fetal medicine specialists, immunologists, transfusion medicine specialists, paediatricians and neonatologists. Using a systematic approach and standardized methodology, the panel developed recommendations for investigations and treatment. Although FNAIT most commonly occurs secondary to anti-HPA-1a antibodies, the recommendations apply, but less strongly, to FNAIT caused by other anti-HPA antibodies. Human leucocyte antigen (HLA) antibodies without HPA antibodies were not considered associated with FNAIT.

Methods

Clinical questions were developed according to the US Preventative Services Task Force Criteria (Harris *et al*, 2001) for antenatal screening and management, diagnostic testing, and postnatal interventions (Appendix S1).

A systematic search for articles published between 1946 and June 2017 in MEDLINE, EMBASE and Cochrane was conducted. Manually searched references of primary articles, relevant reviews and additional articles identified by panel members were included. Conference proceedings were not searched. Search strategies are detailed in Appendix S1. Inclusion criteria were: (i) original data; (ii) five or more pregnancies, fetuses or neonates with or at risk of FNAIT; (iii) and reporting any of the following: mortality, ICH, fetal/neonatal platelet count, proportion transfused or duration of thrombocytopenia.

Two reviewers screened publications for eligibility, independently extracted data and assessed quality and risk of bias of each study using criteria established for the reporting of randomized and non-randomized studies (Fowkes & Fulton, 1991; Higgins *et al*, 2011; Wells *et al*, 2015). The assessment of economic analyses was based on the checklist developed by Evers *et al* (2005). Discrepancies in data collection were resolved by a third reviewer.

Recommendations were formulated based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method which incorporates the quality of the studies, benefits and risks, and resource utilization (Guyatt *et al*, 2011). The level of evidence was graded as strong, moderate, weak or very weak based on the GRADE criteria (Atkins *et al*, 2004). Recommendation strength was evaluated as strong or weak. A strong recommendation was made according to GRADE if the panel was "confident that the desirable effects… outweigh the undesirable effects" (Guyatt *et al*, 2008). A weak recommendation was made if the panel concluded that the "desirable effects … probably outweigh the undesirable effects," but the trade-offs were not well defined (Guyatt *et al*, 2008). Weak recommendations may not be applicable to all patients. The term "should" and "should probably" were used to reflect strong and weak recommendations, respectively.

Web conferences and electronic correspondence were used to discuss the analytic frameworks of the clinical questions, systematic reviews and formulate recommendations. Electronic surveys were sent to all members to assess agreement with recommendations. Disagreements were resolved by group discussions. If disagreements could not be resolved, a recommendation was accepted if the majority (50% or more of the panel) was in agreement. Members recorded their conflicts of interest but none were excluded from voting. Agreements with recommendations were tabulated according to disclosures to ensure biases did not influence decisions.

The final guidance document was sent to maternal fetal, haematology and paediatric societies for feedback (Appendix S3, Table S1). The reviewers from these societies were sent a survey consisting of open and closed-ended

questions to determine agreement with each recommendation, and to identify facilitators and barriers to guideline application. Comments from reviewers were subsequently discussed and addressed by panel members.

The recommendations in this guidance document will be reviewed every 3 years from publication. If a study is published that may impact patients prior to that time, a comment will be added on the ICTMG website (ictmg.org) along with the guideline.

Results

Four systematic reviews (antenatal management, postnatal management, use of HPA alloantibodies to identify pregnancies at risk and the use of HLA genotypes to predict HPA alloimmunization) were developed to support this guideline (Table I) (Winkelhorst *et al*, 2017; Baker *et al*, 2018; Kjaer *et al*, 2018). Characteristics, outcomes, and risk of bias of the studies analysed are described in Appendix S3 (Tables S2–S11). Additional references added following publication of the systematic reviews are detailed in Appendix S4 (Tables S12–S16). Cost effectiveness studies are summarized in Appendix S5 (Tables S17–S19).

The recommendations are categorized as postnatal interventions, antenatal interventions and screening for FNAIT and are summarized in Table II. The administration of intravenous immunoglobulin (IVIG) is detailed in Appendix S6.

Postnatal recommendations

1. **If there is clinical suspicion of fetal and neonatal alloimmune thrombocytopenia (FNAIT), manage as FNAIT without waiting for laboratory confirmation (moderate evidence, strong recommendation).**
2. **If a platelet transfusion is indicated, human platelet antigen (HPA)-selected platelets should be used if immediately available (moderate evidence, strong recommendation).**
3. **If HPA-selected platelets are not immediately available, HPA unselected platelets should be transfused (moderate evidence, strong recommendation).**
4. **Platelets should be transfused immediately if life-threatening bleeding is present (moderate evidence, strong recommendation).**
5. **If an intracranial haemorrhage (ICH) is suspected clinically, do not delay platelet transfusion while awaiting confirmation by imaging studies (very low evidence, strong recommendation).**
6. **In the presence of life-threatening bleeding in a neonate, such as intracranial or gastrointestinal bleeding, platelets should be transfused to maintain platelet counts initially above 100×10^9/l and then above 50×10^9/l for at least 7 days (very low evidence, strong recommendation).**
7. **In the absence of life-threatening bleeding in a neonate, such as intracranial or gastrointestinal bleeding, platelets should be transfused to maintain a platelet count above 30×10^9/l (very low evidence, strong recommendation).**
8. **A cranial ultrasound should be performed to screen for ICH in all neonates suspected of FNAIT within 24 h of delivery (very low evidence, strong recommendation).**
9. **A neonate with FNAIT should have platelet counts monitored until the platelets are normal in the absence of treatment (very low evidence, strong recommendation).**

Table I. References used for guidance on FNAIT.

Guideline topics	Number of citations included	
	Randomized studies	Nonrandomized studies
Postnatal management	0	13
Antenatal management	5	24
Economic Studies for Screening	0	3
HPA alloimmunization	0	15
HLA DRB3*0101 as risk factor for alloimmunization	0	13
Non-invasive prenatal testing	0	3

FNAIT, fetal and neonatal alloimmune thrombocytopenia; HLA, human leucocyte antigen; HPA, human platelet antigen.

Rationale. FNAIT is the most common cause of fetal and neonatal severe thrombocytopenia (platelet count less than 50×10^9/l) and ICH in the first few days of life in a term, otherwise healthy infant (Dreyfus *et al*, 1997; Kaplan, 2001; Chakravorty & Roberts, 2012). FNAIT should also be considered if there is severe neonatal thrombocytopenia even if the thrombocytopenia can potentially be explained by other diagnoses/comorbidities (Bussel *et al*, 2005).

The goal of treating FNAIT is to prevent or minimize major haemorrhage, such as ICH or gastrointestinal bleeding and death. Platelet transfusion (HPA-selected or unselected) is the primary treatment for neonatal thrombocytopenia secondary to FNAIT. Although transfusions lead to reasonable platelet count increments for the neonate, studies are too small to confirm whether platelet transfusions reduce neonatal morbidity and/or mortality (Appendix S3, Table S3). HPA-selected platelet transfusions (maternal or donor) are considered first-line therapy as they result in higher platelet increments and longer duration of response compared to transfusion of unselected platelets. (Baker *et al*, 2018) In one study, platelet counts increased to more than 50×10^9/l in 83% of neonates receiving maternal platelets (19/23) and in 38% (5/13) of thrombocytopenic neonates transfused with HPA-unselected platelets (Mueller-Eckhardt *et al*, 1989). The

Table II. Recommendations for FNAIT interventions.

Postnatal

1. If there is clinical suspicion of FNAIT, manage as FNAIT without waiting for laboratory confirmation (moderate evidence, strong recommendation).
   Balance of harms and benefits: Thrombocytopenia in the neonate may predispose infants to major bleeding (intracranial, gastrointestinal).
   Suggestions for practice: Screen the neonate for intracranial bleeding and transfuse according to recommendations.
   Genotype mother and father for HPAs or the mother and the fetus. Genotyping results are unlikely to be available immediately.
2. If a platelet transfusion is indicated, HPA-selected platelets should be used if immediately available (moderate evidence, strong recommendation).
3. If HPA-selected platelets are not immediately available, HPA unselected platelets should be transfused (moderate evidence, strong recommendation).
4. Platelets should be transfused immediately if life-threatening bleeding is present (moderate evidence, strong recommendation).
   Balance of harms and benefits: Waiting for HPA-typed platelets may be associated with poorer outcomes.
   Suggestions for practice: If a platelet transfusion is indicated for the neonate and if HPA selected platelets are not immediately available, HPA non-selected platelets should be transfused. If HPA-1a negative platelets are transfused and if the platelet increment is inadequate, look for other HPA discrepancies. Platelets do not need to be HLA typed. In the rare circumstance where either HPA unselected or HPA selected platelets are not available; infuse the neonate with IVIG 1 g/kg. If there is a response to IVIG, it will not occur before 24–72 h whereas the neonate requires an increment immediately if there is bleeding or if the platelet count is less than 30×10^9/l. If maternal platelets are transfused to the neonate, they should be washed to remove HPA antibody and irradiated to prevent transfusion-associated graft-versus-host disease. Irradiation of the platelet product should not delay administration. The standard dose of platelets in accordance with local and national guidelines is warranted.
5. If an ICH is suspected clinically, do not delay platelet transfusion while awaiting confirmation by imaging studies (very low evidence, strong recommendation).
6. In the presence of life-threatening bleeding in a neonate, such as intracranial or gastrointestinal bleeding, platelets should be transfused to maintain platelet counts initially above 100×10^9/l and then above 50×10^9/l for at least 7 days (very low evidence, strong recommendation).
7. In the absence of life-threatening bleeding in a neonate, such as intracranial or gastrointestinal bleeding, platelets should be transfused to maintain a platelet count above 30×10^9/l (very low evidence, strong recommendation).
8. A cranial ultrasound should be performed to screen for ICH in all neonates suspected of FNAIT within 24 h of delivery (very low evidence, strong recommendation).
9. A neonate with FNAIT should have platelet counts monitored until the platelets are normal in the absence of treatment (very low evidence, strong recommendation).

Antenatal

10. Women with FNAIT in a previous pregnancy or sisters of women with FNAIT should be referred to fetal medicine centres (very low evidence, strong recommendation).
11. Fetal HPA typing, preferably using non-invasive methods, if adequately quality assured, should be performed during pregnancy when the father is unknown, unavailable for testing or heterozygous for the implicated antigen (moderate evidence, strong recommendation).
    Balance of harms and benefits: The alternative is amniocentesis, which is associated with risk of fetal demise.
    Suggestions for practice: If the father is homozygous for the antigen in question, the fetus should be presumed to be affected. If the father is heterozygous, 50% of the fetuses will be affected. If the father is heterozygous or antigen typing for the father is not available, fetal genotype can be determined by assessing cell free fetal DNA for HPA-1a or by typing of amniocyte DNA. Samples for non-invasive prenatal testing can be sent to Sanquin (Netherlands) or Tissue and Blood Banks (Barcelona, Spain).
12. In patients identified by screening or sisters of patients with FNAIT, the presence and/or concentration of HPA antibodies in subsequent pregnancies may be useful to determine the risk of FNAIT (low evidence, weak recommendation).
13. Consecutive assessments of levels of anti-HPA-1a antibody in HPA-1a-immunised women, using the MAIPA, may be useful in identifying the risk of FNAIT. Antibody levels should be expressed in IU/ml, not as titres, if used for this purpose (low evidence, weak recommendation).
14. HLA DRB3*01:01 typing of HPA-1b1b women (including sisters) considering pregnancy should be used to identify women who have a low risk of developing anti-HPA-1a antibodies (moderate evidence, strong recommendation).
15.* Antenatal IVIG administration to the mother, commencing at 12–16 weeks gestation, should be offered to all women in a subsequent pregnancy with maternal fetal incompatibility who have had a previous fetus or neonate with FNAIT-related ICH (very low evidence, strong recommendation).
    Balance of harms and benefits: Benefits outweigh harms. Maternal administration of IVIG appears to reduce the risk of fetal/neonatal ICH. The frequency of minor adverse events to IVIG in the maternal population is not increased compared to the non-pregnant population.
    Suggestions for practice: IVIG 1 g/kg/week at 12–16 weeks, increase to 2 g/kg/week at 20 weeks or IVIG 1 g/kg at 12–16 weeks, add corticosteroids at 1 mg/kg/day at 20 weeks or IVIG 0·5 g/kg at 12–16 weeks for the entire pregnancy or IVIG 2 g/kg/week at 12–16

Table II. (*Continued*)

weeks for the entire pregnancy or IVIG 2 g/kg/week at 12–16 weeks, add corticosteroids 1 mg/kg/day at 20 weeks. If 2 g/kg/week is used, as this is a high dose, mothers should be monitored for haemolysis, particularly if the patient is blood group A, AB or B, as higher doses of IVIG are associated with increased risk of IVIG-associated haemolysis.

16.* For all other pregnancies with a previous neonate with FNAIT (without ICH), administering antenatal IVIG to the mother should be discussed prior to a subsequent pregnancy or when pregnancy with maternal fetal incompatibility is confirmed (very low evidence, strong recommendation).

a. If antenatal intervention is required, IVIG administration to the mother should be started between 20 and 22 weeks (and not later than 24 weeks) gestation (very low evidence, strong recommendation).

Balance of harms and benefits: IVIG appears to reduce the risk of fetal/neonatal ICH. The frequency of adverse events to IVIG in the maternal population is not increased compared to the non-pregnant population.

Suggestions for practice: IVIG 1 g/kg/week, IVIG 2 g/kg/week, IVIG 1 g/kg/week and corticosteroids 1 mg/kg/day administered to the mother are options for treatment. If 2 g/kg/week is used, as this is a high dose, patients should be monitored for haemolysis, particularly if the patient is blood group A, AB or B, as higher doses of IVIG are associated with increased risk of IVIG-associated haemolysis.

17. If corticosteroids are used with IVIG, dexamethasone should not be used because of the associated risk of oligohydramnios (low evidence, strong recommendation).

Delivery

18. If the fetal platelet count is unknown, a planned delivery should be performed (very low evidence, strong recommendation).

Balance of harms and benefits: Early delivery is associated with higher risks of fetal complications.

Suggestions for practice: Delivery at more than 37 weeks is suggested in the absence of suspected fetal thrombocytopenia. The risk of haemorrhage has not been well described. Fetal platelet counts less than 50×10^9/l in very experienced centres have not been associated with increased risk of bleeding. HPA-selected platelets should be available at the time of delivery for the neonate.

19. If the fetal platelet count is unknown, assisted delivery and invasive procedures on the fetus during delivery should be avoided, including forceps, vacuum-assisted delivery, scalp blood sampling and scalp electrodes (very low evidence, strong recommendation).

20. A cord blood sample should be sent for platelet count determination immediately after delivery (low evidence, strong recommendation).

21. HPA-selected platelets should be available at the time of delivery (low evidence, strong recommendation).

Balance of harms and benefits: HPA-selected platelets are associated with higher platelet increments in the neonate compared to non HPA-selected platelets. If delivery is not planned, HPA-selected platelets may not be readily available.

Suggestions for practice: HPA-selected platelets should be available at the time of delivery, if feasible. HPA-selected are defined as platelets having the same HPA genotype/phenotype of the implicated antigen as the mother. Otherwise HPA non-selected platelets should be available. Some centres ensure that red blood cells negative for the implicated HPA antigen are available for the mother in case she has bleeding, to reduce the risk of the mother developing post-transfusion purpura.

Screening

22. All pregnant women should probably be screened for HPA-1b1b in their first pregnancy if the cost effectiveness of detection is acceptable and a management scheme is in place (low evidence, weak recommendation).

Balance of harms and benefits: Screening may detect women at increased risk of adverse pregnancy outcomes. Screening may expose women to unnecessary antenatal intervention. The clinical and cost effectiveness has not been established.

Suggestions for practice: If HPA incompatibility is identified in pregnancies by screening, women should be directed to comprehensive care centres. HPA alloantibody determination and HLA haplotypes for HPA-1 incompatibility can be used antenatally to determine risk and guide antenatal intervention. If an HPA alloantibody is present, serial titres may be useful to determine risk, e.g. increasing titres are associated with a risk of FNAIT. If an HPA-1a alloantibody is not present, HLA haplotypes may be used determine risk of alloimmunization. The absence of HLA DRB3*01:01 is associated with very low risk of FNAIT. Alternatively, platelet products are made available on the day of delivery and neonatal platelet counts are determined immediately following delivery to determine if there is a need for platelet transfusion if antenatal intervention is not offered.

FNAIT, fetal and neonatal alloimmune thrombocytopenia; HLA, human leucocyte antigen; HPA, human platelet antigen; ICH, intracranial haemorrhage; IVIG, intravenous immunoglobulin; MAIPA, monoclonal antibody immobilization of platelet antigen assay.
*Please see Appendix S6 for clinical considerations regarding administration of IVIG.

half-life of transfused HPA-1a/5b selected platelets was estimated to be twice that of unselected platelets (1·9 vs. 1 day) (Allen *et al*, 2007). If HPA-selected platelets are unavailable immediately, unselected platelets should be provided to bridge the time until HPA-selected platelets are available. Given that anti-HPA-1a and anti-HPA-5b are implicated in more than 95% of clinically diagnosed cases of FNAIT in Caucasians, blood establishments may attempt to maintain a HPA-1a, -5b negative platelet inventory (Allen *et al*, 2004).

The optimal threshold at which to transfuse platelets prophylactically to neonates to prevent bleeding has not been determined. Thresholds for platelet transfusion have ranged from 5×10^9/l to 100×10^9/l (te Pas *et al*, 2007; Bassler *et al*, 2008; Sachs, 2013; Gunnink *et al*, 2014). Only two studies

indicated a platelet count for transfusion (35 and 50 $\times$ 10^9/l) and neither assessed the effect on bleeding (Kjeldsen-Kragh *et al*, 2007; te Pas *et al*, 2007). In our systematic review, the platelet count (at birth or nadir) was found to be less than 30 $\times$ 10^9/l in 24 of the 29 neonates with ICH for whom platelet counts were reported. Platelet counts were not available in the other 34 neonates with ICH (Baker *et al*, 2018). Thus, a transfusion threshold of less than 30 $\times$ 10^9/l was considered reasonable for prophylactic platelet transfusion. Higher thresholds in the presence of ICH (50–100 $\times$ 10^9/l) were deemed necessary to reduce the risk of further haemorrhage. These thresholds may also be higher in preterm or sick neonates at risk for ICH.

Administration of intravenous immunoglobulin (IVIG) to the neonate could be considered in the following scenarios: in the presence of ICH or other life-threatening bleeding and/or platelet count <30 $\times$ 10^9/l if platelet products are unavailable. The platelet count increase in the neonate (if it occurs) may take 24–72 h following IVIG infusion when given alone. Given limited data supporting its efficacy as an adjunct agent, as well as potential side effects from IVIG (including haemolysis in non-group O neonates and neutropenia) (Majer & Green, 1988; Veys *et al*, 1988; Singh-Grewal *et al*, 2006; Khan *et al*, 2010; Krishnan & Pathare, 2011; Luban *et al*, 2015; Akman *et al*, 2017), IVIG was not considered in addition to platelet transfusion.

Corticosteroids have also been used in combination with platelet transfusion and/or IVIG in a limited number of neonates (n = 10), where a change in platelet count was provided for assessment (Lee *et al*, 2002; Fratellanza *et al*, 2006; Kiefel *et al*, 2006). The effectiveness of the addition of corticosteroids from these limited data is uncertain.

Urgent head ultrasound (HUS) examination is essential when FNAIT is clinically suspected, to exclude ICH. Magnetic resonance imaging (MRI) may be performed if needed to confirm or identify an ICH or to determine its age; MRI may be performed without sedation (Kovanlikaya *et al*, 2017).

The typical nadir platelet count for FNAIT occurs within 48 h of delivery (Kiefel *et al*, 2006), and most infants recover within 1–5 weeks (Galea *et al*, 1981). In rare cases, thrombocytopenia may persist for 8 weeks or longer; therefore platelet counts should be followed regularly until counts normalize (Chakravorty & Roberts, 2012). If platelet counts do not normalize within a reasonable timeframe, alternative diagnoses, such as congenital thrombocytopenia, should be considered.

Antenatal recommendations

10. **Women with FNAIT in a previous pregnancy or sisters of women with FNAIT should be referred to fetal medicine centres (very low evidence, strong recommendation).**
11. **Fetal HPA typing, preferably using non-invasive methods, if adequately quality assured, should be performed during pregnancy when the father is unknown, unavailable for testing, or heterozygous for the implicated antigen (moderate evidence, strong recommendation).**
12. **In patients identified by screening or sisters of patients with FNAIT, the presence and/or concentration of HPA antibodies in subsequent pregnancies may be useful to determine the risk of FNAIT (low evidence, weak recommendation).**
13. **Consecutive assessments of levels of anti-HPA-1a antibody in HPA-1a-immunized women, using the monoclonal antibody immobilization of platelet antigen (MAIPA) assay, may be useful in identifying risk of FNAIT. Antibody levels should be expressed in IU/ml and not as titres if used for this purpose (low evidence, weak recommendation).**
14. **HLA DRB3*01:01 typing of HPA-1b1b women (including sisters) considering pregnancy should be used to identify women who have a low risk of developing anti-HPA-1a antibodies (moderate evidence, strong recommendation).**
15. **Antenatal intravenous immunoglobulin (IVIG) administration to the mother, commencing at 12–16 weeks gestation, should be suggested to all women in a subsequent pregnancy with maternal fetal incompatibility who have had a previous fetus or neonate with FNAIT-related ICH (very low evidence, strong recommendation).**
16. **For all other pregnancies with a previous neonate with FNAIT (without ICH), administering antenatal IVIG to the mother should be discussed prior to a subsequent pregnancy or when pregnancy with maternal fetal incompatibility is confirmed (very low evidence, strong recommendation).**
    a. **If antenatal intervention is required, IVIG administration to the mother should be started between 20 and 22 weeks (and not later than 24 weeks) gestation (very low evidence, strong recommendation).**
17. **If corticosteroids are used with IVIG, dexamethasone should not be used because of the associated risk of oligohydramnios (low evidence, strong recommendation).**

Rationale. The risk of recurrence of FNAIT in subsequent antigen-incompatible pregnancies is significant. In women with a previous infant with ICH, the recurrence rate of ICH has been reported to be 72% (95% confidence interval [CI] 46–98%) without the inclusion of fetal deaths, and 79% (95% CI 61–97%) with their inclusion (Radder *et al*, 2003). Mothers of mildly affected or undiagnosed first-born children with HPA-1b1b can have severely affected children (Bussel *et al*, 1997; Bussel & Kaplan, 1998). In first pregnancies without an ICH, the risk of ICH in the second affected pregnancy appears to be low, but there are little data on untreated second pregnancies. Thus, antenatal intervention for subsequent pregnancies should be carefully discussed in centres with expertise in FNAIT.

Determining fetal antigens

Non-invasive prenatal testing (NIPT), available in some centres, using cell-free fetal DNA (cffDNA) can determine whether the fetus carries the HPA-1a gene if the biological father is heterozygous for the HPA antigen or unavailable for testing (Appendix S4, Tables S4 and S5) (Scheffer *et al*, 2011; Le Toriellec *et al*, 2013). Although only two studies assessed cffDNA for HPA-1, there were no false positive or false negative results in the 63 samples screened. The primary alternative is amniocentesis with its associated risks of pregnancy loss of 0·5–1·0% (Wilson *et al*, 2015). Chorionic villus sampling increases the risk of alloimmunization and fetal loss (Moise & Carpenter, 1990; Akolekar *et al*, 2015). Preimplantation genetic diagnosis with selection of embryos that are HPA-1b1b and *in vitro* fertilization with sperm donors that are HPA-1b1b have been described (Altarescu *et al*, 2012; Tiller *et al*, 2016a).

HPA alloimmunization

Only 10% of women who are HPA-1b1b have detectable HPA-1a alloantibodies despite carrying a fetus with HPA-1a (Kamphuis *et al*, 2010). On the other hand, severe neonatal thrombocytopenia has been described in HPA-1b1b women who do not have demonstrable alloantibodies (Bussel *et al*, 1988; Arnold *et al*, 2008).

The monoclonal antibody immobilization of platelet antigen (MAIPA) assay has been widely used to detect alloantibodies; other assays have not been shown to be as reliable (Kjaer *et al*, 2018). Prospective screening studies of unselected pregnancies (~125 000 women) showed that among HPA-1a-immunized pregnancies ($n = 216$), high levels of anti-HPA-1a antibodies in the third trimester or at delivery correlated with low platelet counts in the neonate (Williamson *et al*, 1998; Killie *et al*, 2008). This suggests that maternal HPA-1a antibody level in the third trimester may have potential utility as a predictive tool for patients identified by generalized screening (Kjaer *et al*, 2018). The negative predictive value (NPV) of a titre of 32 or concentration of 3 IU/ml and a neonatal platelet count $<50 \times 10^9$/l was 88% (Williamson *et al*, 1998) to 95% (Killie *et al*, 2008) when the antibody was determined in the third trimester or at delivery, respectively. For subsequent pregnancies, maternal anti-HPA-1a antibody level in the second trimester correlated with second trimester fetal platelet counts. The NPVs for cut-off levels 23–31 IU/ml and fetal/neonatal platelet count $<20–50 \times 10^9$/l ranged from 60% to 86% (Bertrand *et al*, 2006, 2014; Ghevaert *et al*, 2007a).

HLA genotyping

Several studies have demonstrated a strong association between HLA DRB3*01:01 and risk of HPA-1a-immunization in FNAIT. Absence of HLA DRB3*01:01 in a maternal-fetal incompatible pregnancy is associated with a very low risk of alloimmunization. Nine of 13 studies reviewed described this association (Appendix S4, Tables S8–S10) (Mueller-Eckhardt *et al*, 1985; Blanchette *et al*, 1990; L'Abbe *et al*, 1992; Williamson *et al*, 1998; Maslanka *et al*, 2003; Turner *et al*, 2005; Kjeldsen-Kragh *et al*, 2007; Killie *et al*, 2008; Sainio *et al*, 2017; Wienzek-Lischka *et al*, 2017). The positive predictive values (PPVs) and NPVs in three studies ranged from 17–35% and 96–100% respectively (Williamson *et al*, 1998; Maslanka *et al*, 2003; Turner *et al*, 2005). Overall, HLA DRB3*01:01 typing was considered useful in determining absence of risk of HPA alloimmunization in women who are HPA-1b1b and have neither had an affected infant nor detectable HPA-1a alloantibodies. Biomarkers are needed for other HPA discordances.

Determination of fetal antigens by NIPT, HPA phenotype and genotype as well as presence of HPA antibody and HLA genotype should be performed by experienced laboratories.

Non-invasive antenatal management strategies

Centres differ on the optimal antenatal algorithm for FNAIT. Historically, fetal blood sampling (FBS) and intrauterine transfusion (IUT) were offered to many women. Antenatal interventions now commonly include IVIG and corticosteroids administered to the mother or combined treatment. Previous studies reported that in 50% of 107 subsequent fetuses of previous severely affected pregnancies, the fetal platelet count was 20×10^9/l or less by 24 weeks of gestation (Bussel *et al*, 1997). Accordingly, antenatal maternal treatment with IVIG with or without steroids is provided by some centres if there is a previous severely affected pregnancy and a current maternal-fetal incompatible pregnancy. In contrast, for HPA-1a-immunized women initially identified by screening, Tiller *et al* (2016b) found that neonatal platelet counts increased or were unchanged in 70% of 45 untreated subsequent pregnancies. Thus, in Norway, where women are screened for FNAIT, antibody concentration has been used to guide maternal antenatal treatment and only a small proportion of pregnancies at risk are treated with IVIG. These differences probably reflect pregnancies that are identified by screening compared to pregnancies with a previously affected fetus/neonate.

Our systematic review identified four randomized controlled trials (RCTs) and 22 nonrandomized studies addressing antenatal intervention with IVIG and/or corticosteroids. Following publication of the systematic review (Winkelhorst *et al*, 2017), three additional studies were included: one RCT and two observational studies (Kamphuis *et al*, 2016, 2017; Lakkaraja *et al*, 2016). Overall, in mothers treated with IVIG, four neonatal ICHs occurred in 315 pregnancies. None of the studies, however, were large enough to detect a difference in ICH or mortality among treatment regimens. None of the regimens in the randomized studies were compared to placebo because not offering treatment has been considered unethical.

Nonetheless, antenatal IVIG administered to the mother resulted in an increased fetal or neonatal platelet count.

Randomized studies have not carefully addressed the dose, gestational age at which to initiate maternal IVIG, the duration of IVIG use and adverse events secondary to IVIG. In most studies, IVIG was administered to pregnant women at 1 g/kg/week. Doses included, often in single studies, 0·4 g/kg/day for 5 days, 0·5 g/kg/week, 0·8 g/kg/week, 1 g/kg every 2 weeks and 2 g/kg/week. Although data are limited, antenatal maternal use of IVIG did not appear to affect fetal/neonatal growth and development, incidence of infection or neuropsychological development. (Radder *et al*, 2004; Ward *et al*, 2006) Appendix S6 describes potential regimens for antenatal treatment.

Maternal treatment with corticosteroids has been assessed in multiple studies; four studies used corticosteroids alone (Kaplan *et al*, 1998; Berkowitz *et al*, 2006; Ghevaert *et al*, 2007b; Bertrand *et al*, 2011) and 12 studies combined corticosteroids and IVIG with or without IUT (Lynch *et al*, 1992; Murphy *et al*, 1994; Bussel *et al*, 1996, 2010; Berkowitz *et al*, 2006, 2007; Bertrand *et al*, 2006, 2011; Ghevaert *et al*, 2007b; Mechoulan *et al*, 2011; Lakkaraja *et al*, 2016; Kamphuis *et al*, 2017). Prednisone and dexamethasone dosages administered to the mother were predominantly 0·5 mg/kg/day and 1·5 mg/day, respectively. In one study, maternal administration of corticosteroids alone resulted in similar neonatal platelet increments compared to maternal administration of IVIG in pregnancies that did not have a previous pregnancy with fetal/neonatal ICH secondary to FNAIT and had an initial fetal platelet count >20 $\times$ 10^9/l (Berkowitz *et al*, 2006). The studies that compared maternal IVIG alone with maternal IVIG and corticosteroids noted similar fetal/neonatal platelet counts with either regimen except for three studies (Bussel *et al*, 1996, 2010; Bertrand *et al*, 2011). Five of 10 fetuses who had failed maternal IVIG 1 g/kg/week alone or in combination with dexamethasone had a mean increment in platelet count of 65·2 $\times$ 10^9/l with the addition of prednisone administered to the mother in one study (Bussel *et al*, 1996). Consequently, in a RCT reported by Bussel *et al* (2010), prednisone was added to the mother's regimen if fetuses did not have a satisfactory response to maternal administration of 2 g/kg/week of IVIG in pregnancies where the previous fetus/neonate had an ICH. The platelet counts in five neonates were above 50 $\times$ 10^9/l with the addition of prednisone to the maternal IVIG regimen. Bertrand *et al* (2011), in a non-randomized study, reported a significant difference in the number of newborns needing postnatal treatment: 26% with the maternally administered IVIG and corticosteroids, versus 59% with maternal IVIG alone (P = 0·01). No statistically significant differences in the mean neonatal platelet count or severe thrombocytopenia were observed (Bertrand *et al*, 2011). The highest mean newborn platelet count for a combination of maternal IVIG and corticosteroids was 135 $\times$ 10^9/l compared to 89 $\times$ 10^9/l with maternal IVIG use alone. The proportion of newborns with severe thrombocytopenia (less than 50 $\times$ 10^9/l) was 27% with the use of maternal IVIG and corticosteroids and 44% with the use of maternal IVIG alone. Maternal treatment with dexamethasone at a dose of 3–5 mg/day has been associated with oligohydramnios and was not effective at a dose of 1·5 mg daily when added to IVIG (Lynch *et al*, 1992; Bussel *et al*, 1996).

The ideal gestational age at which to initiate non-invasive treatment to the mother is unknown. The time to initiate maternal IVIG has been described to range from 12 to 32 weeks in the studies identified (Winkelhorst *et al*, 2017). The aim is to prevent fetal/neonatal ICH and its potential associated complications. Approximately 54% of fetal ICHs have been described to occur before gestational week 28 (Tiller *et al*, 2013). As fetal platelet antigens are expressed and may enter the mother's circulation at, or even earlier than, 16 weeks gestation,(Gruel *et al*, 1986) IVIG administered to the mother is most commonly commenced at 12–16 weeks gestation in women who had a previously affected infant with ICH, and, in the absence of a previous ICH, at 20–24 weeks gestation. The optimal duration of IVIG administration to the mother has not been determined but treatments are commonly continued throughout pregnancy.

Invasive strategies

Fetal blood sampling (FBS) is not commonly performed because complication rates as high as 11% have been reported; 25% of the time leading to fetal or neonatal loss (Winkelhorst *et al*, 2017). The most frequent complication has been the need for an emergency Caesarean section (C-section) mainly due to fetal distress, of which approximately half resulted in a delivery before 34 weeks gestation (Winkelhorst *et al*, 2017). If FBS is considered, it should *only* be performed by invasive fetal medicine specialists.

Delivery recommendations

18. **If the fetal platelet count is unknown, a planned delivery should be performed (very low evidence, strong recommendation).**
19. **If the fetal platelet count is unknown, assisted delivery and invasive procedures on the fetus during delivery should be avoided, including forceps, vacuum-assisted delivery, scalp blood sampling and scalp electrodes (very low evidence, strong recommendation).**
20. **A cord blood sample should be sent for platelet count determination immediately after delivery (low evidence, strong recommendation).**
21. **HPA-selected platelets should be available at the time of delivery (low evidence, strong recommendation).**

Rationale. There are no trials evaluating the most appropriate mode of delivery and C-section and vaginal deliveries are

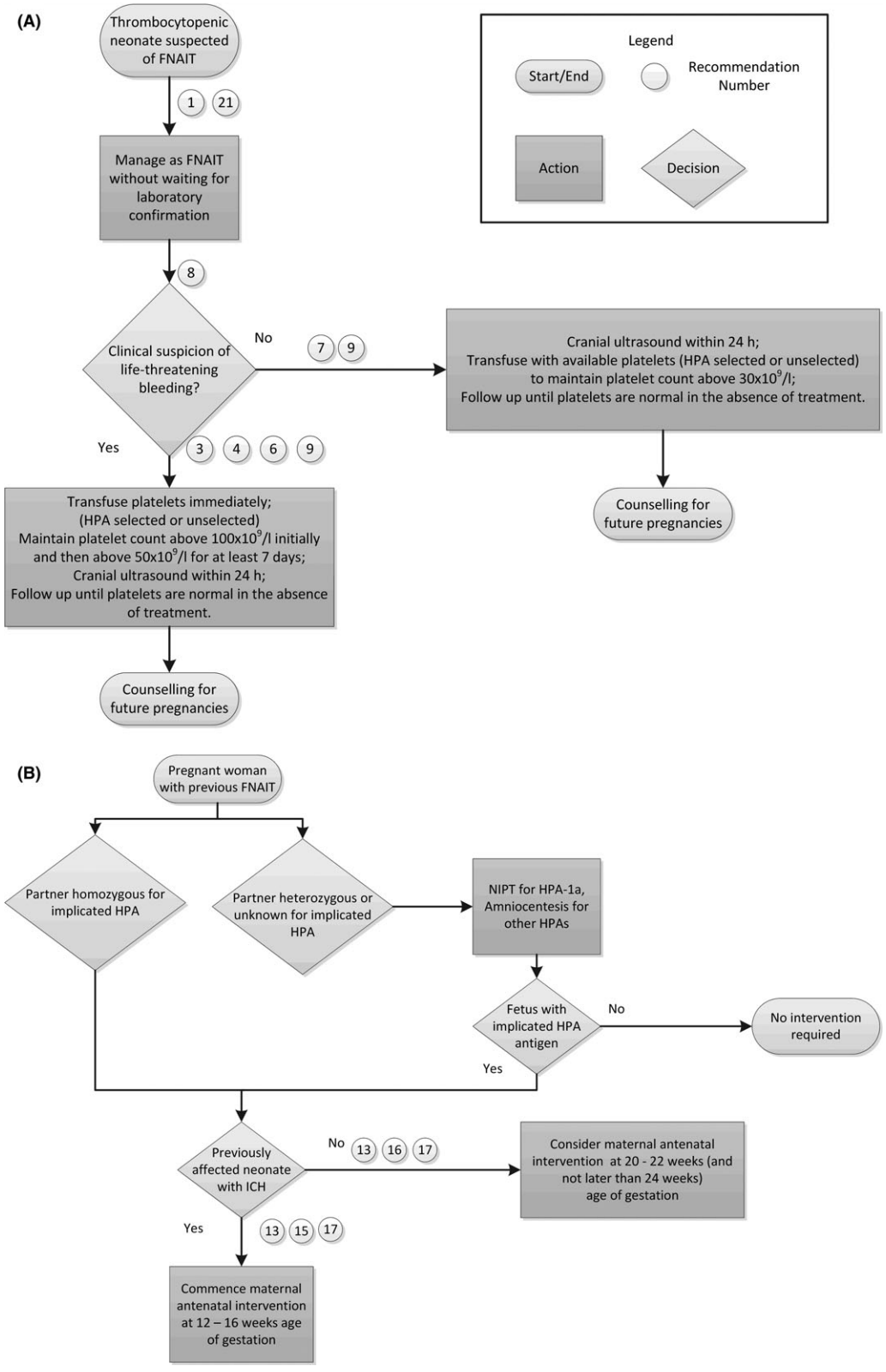

Fig 1. (A) Postnatal Algorithm for FNAIT. (B) Antenatal Algorithm for FNAIT. Please see Table II for potential treatment algorithms. FNAIT, fetal and neonatal alloimmune thrombocytopenia; HLA, human leucocyte antigen; ICH, intracranial haemorrhage; NIPT, non-invasive prenatal testing.

used at different centres internationally. A prospective study of 200 pregnancies with FNAIT identified that all 17 postnatal ICHs occurred within 24 h of delivery, suggesting delivery-related trauma may have triggered neonatal ICH (Ghevaert *et al*, 2007b). Elective C-section is used routinely in some centres for very high risk patients, especially those who have had a previous fetus/neonate with ICH, high level of anti-HPA-1a antibodies (>3 IU/ml), and/or patients who have never delivered vaginally. A prospective study assessing the safety of delivery for FNAIT pregnancies reported that 72% (23/32) of the mothers delivered vaginally and no neonates suffered ICH. Of note, four neonates had severe thrombocytopenia and three were delivered vaginally (van den Akker *et al*, 2006). Vaginal birth remains an option, especially for women with a history of uncomplicated vaginal birth.

FBS with platelets available is offered by some fetal medicine centres experienced in invasive fetal procedures to determine mode of delivery, e.g. to allow induction of labour and vaginal delivery immediately after *in utero* platelet transfusion to ensure the post-transfusion platelet count is above 50×10^9/l.

A planned delivery permits for the availability of HPA-selected platelets at the time of delivery. A lower rate of FNAIT-related adverse events has been reported when neonates were delivered with early C-section and antigen-negative platelets were immediately administered (Kjeldsen-Kragh *et al*, 2007), demonstrating the benefit of having antigen–negative platelets available at delivery. Procedures, such as forceps, vacuum-assisted delivery, scalp blood sampling and scalp electrodes should be avoided as they potentially increase the risk of bleeding in a thrombocytopenic fetus.

Universal maternal HPA screening recommendation

22. **All pregnant women should probably be screened for HPA-1b1b in their first pregnancy if the cost effectiveness of detection is acceptable and a management scheme is in place (low evidence, weak recommendation).**

Rationale. The current management of pregnancies with FNAIT depends predominantly on the identification of a fetus/neonate with thrombocytopenia, with or without ICH, confirmed by laboratory testing. Ideally, pregnancies at risk should be identified *a priori* to reduce the risk of ICH. Currently, pregnancies are not routinely screened for HPA because of uncertainty regarding the optimal antenatal approach if an HPA discrepancy is identified, the absence of defined prophylaxis and cost effectiveness. Three studies assessed cost effectiveness of screening all pregnant women for HPA-1a associated FNAIT (Appendix S6, Tables S17–S19) (Durand-Zaleski *et al*, 1996; Turner *et al*, 2005; Killie *et al*, 2007). The screening algorithms differed. One considered costs for three screening algorithms that varied by whether an HPA antibody was present, the concentration of the antibody and presence of HLA DRB3*01:01 (Killie *et al*, 2007). Postnatal screening of neonates for thrombocytopenia was compared to maternal screening in the second study (Durand-Zaleski *et al*, 1996). Lastly, maternal HPA-1a screening followed by genotyping of the partners was analysed according to whether mothers had HPA antibodies (Turner *et al*, 2005). The analyses varied in the frequency of antibody testing, inclusion of antenatal IVIG, cost of investigation, treatment of neonates, inclusion of long-term costs of neurological disability and the disutility of informing mothers their fetuses had a discordant platelet antigen. Screening was considered to be potentially cost effective if the cost of HPA-1a typing, diagnostic accuracy of antibody and/or HLA DRB3*01:01 determination to direct antenatal intervention, and cost of antenatal intervention, were within acceptable expenditures of health care systems, with the caveat that the optimal antenatal approach to prophylaxis and treatment is unknown. Generalized screening does not apply to sisters of females with FNAIT as they should be screened.

Discussion

The intent of this guidance document is to facilitate identification and management of FNAIT. Based on recommendations in this document, we developed algorithms (Fig 1), separate podcasts for physicians and patients, pamphlets for patients, and a slide set to guide practice (available at ictmg.org).

There continues to be a pressing need for additional collaborative research for FNAIT. Antenatal and postnatal strategies need further optimization. The use of HPA-1a antibody concentration and biomarkers to guide antenatal management needs continued exploration. Morbidity resulting from the psychological stress of families at risk for FNAIT has yet to be addressed in any study. Reducing the morbidity and mortality of FNAIT and its treatments remains a priority, as does the development of screening algorithms to prevent occurrence of FNAIT.

Disclaimer

The International Collaboration for Transfusion Medicine Guidelines' ("ICTMG") guidelines are prepared by ICTMG guideline development groups and are approved by ICTMG membership. The ICTMG guidelines should be used in the context of applicable medical, legal and ethical requirements in any individual case.

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Author contributions

T.B. and E.M identified and selected studies following publications of systematic reviews. N.S extracted data and assessed methodologic quality and bias. L.L. and N.S. drafted the guideline manuscript. N.S. and L.L. take responsibility for the accuracy and integrity of all of the data. All authors contributed to the development of recommendations, revision of recommendations, response to external reviewers, the development of the podcast and patient page, and critically reviewing the manuscript and approval of the final version.

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MK and JKK are two of the founders and owners of Prophylix Pharma AS, a Norwegian biotech company coordinating the EU-funded PROFNAIT Consortium, which is developing a prophylaxis against fetal and neonatal alloimmune thrombocytopenia. NS and DA are consultants for Canadian Blood Services. DO has received research funding to a project "Towards routine HPA-screening in Pregnancy". JB is a consultant of Baxalta, Superior Biologics. HS is a member of the Neonatal Alloimmune Thrombocytopenia Registry of the Transfusion Outcomes Research Collaborative (TORC), Australia. The remaining authors declare that they have no conflicts of interest.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Main question for postnatal management and Main question for antenatal management.

Appendix S2. Search strategies.

Appendix S3. External reviewers and Evidence tables.

Appendix S4. References identified following publications of the ICTMG systematic reviews.

Appendix S5. Economic studies.

Appendix S6. Suggestions for Clinical Practice.

Table S1. External reviewers.

Table S2. GRADE evidence profile for antenatal intervention.

Table S3. GRADE evidence profile for postnatal intervention.

Table S4. Characteristics of nonrandomized studies assessing non-invasive prenatal testing.

Table S5. Risk of bias of nonrandomized studies assessing non-invasive prenatal testing.

Table S6. GRADE evidence profile for detection of maternal anti-HPA-1a antibody in screening studies of unselected pregnant women.

Table S7. GRADE evidence profile for detection of maternal anti-HPA-1a antibody presence in 2nd and 3rd trimester of known or suspected FNAIT cases.

Table S8. Characteristics of nonrandomized studies addressing maternal HLA DRB3*01:01 as risk factor for maternal alloimmunization to HPA-1a.

Table S9. Outcomes of nonrandomized studies addressing maternal HLA DRB3*01:01 as risk factor for maternal alloimmunization to HPA-1a.

Table S10. Quality of nonrandomized studies addressing maternal HLA DRB3*01:01 as risk factor for maternal alloimmunization to HPA-1a.

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Table S12. Characteristics and outcomes of randomized and nonrandomized studies of antenatal intervention administered

to the mother identified following the publication of the ICTMG systematic review for antenatal intervention.

Table S13. Assessment of the risk of bias of the randomized controlled study identified following the publication of the ICTMG systematic review for antenatal intervention.

Table S14. Assessment of the risk of bias of the nonrandomized studies identified following publication of the ICTMG systematic review for antenatal intervention.

Table S15. Characteristics and outcomes of the use of maternal HPA alloantibody for screening or from known or suspected FNAIT patients identified following publication of the ICTMG systematic review.

Table S16. Quality of nonrandomized studies of maternal HPA alloantibody detection from known or suspected FNAIT patients following publication of the ICTMG systematic review.

Table S17. Characteristics of economic studies addressing antenatal maternal screening for FNAIT.

Table S18. Outcomes of economic studies addressing antenatal maternal screening for FNAIT.

Table S19. Quality of economic studies.

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