Prenatal Management of Pregnancies at Risk of Fetal Neonatal Alloimmune Thrombocytopenia (FNAIT)

1. Introduction

Fetal neonatal alloimmune thrombocytopenia (FNAIT), also known as neonatal alloimmune thrombocytopenia (NAIT) or fetomaternal alloimmune thrombocytopenia (FMAIT), is a rare but serious condition associated with significant fetal and neonatal morbidity and mortality. As the condition can affect the neonate and/or the fetus, the term FNAIT is used in this paper. The condition is defined by the presence of maternal alloantibodies directed against antigens present on the fetal and neonatal platelets. These antigens are inherited from the father (or from donor gametes, including the egg or sperm, during in vitro fertilisation) and are thus absent on the maternal platelets. The antibodies created cross the placenta and attack the fetal platelets.

The most useful predictor of severe disease is a history of a sibling with an antenatal intracranial haemorrhage (ICH). However, FNAIT can occur during the first pregnancy and may not be diagnosed until the neonatal period. The incidence of FNAIT is approximately 1 in 1000 pregnancies. FNAIT is suspected in a neonate with thrombocytopenia for which there is no other medical cause identified. In mild to moderately affected neonates FNAIT typically resolves in the first week of life without any sequelae, however in severely affected neonates with extensive ICH (up to 20% of cases) this disorder can lead to death or serious neurological sequelae.

The diagnosis depends on demonstrating maternal/neonatal or maternal/paternal platelet antigen incompatibility with a maternal antibody to a paternal antigen. The most commonly detected antibodies in Caucasians are those directed against human platelet antigen (HPA)-1a (80%) and HPA-5b (10–15%), which can allow prediction of at-risk fetuses. Where results are not supportive but clinical suspicion of FNAIT is high, further testing and management should be discussed with the diagnostic laboratory.

The prenatal management of FNAIT has undergone a major shift over the past few years. There has been an increase in the use of immunoglobulins following evidence of probable efficacy, and as a consequence, reduced use of invasive fetal testing and fetal blood sampling (FBS).

There is very little high quality evidence on which to base management of this condition, but advances in treatment report very good outcomes. As FNAIT is very rare, the treatments are costly and adverse consequences for the fetus potentially disastrous. This document considers the latest evidence in relation to treatment options in the prenatal management of pregnancies at risk of FNAIT; specifically, the role of screening, immunoglobulins, steroids, FBS and intrauterine platelet transfusion. Moreover, whether scientific research has shown treatments to be of benefit to women and their babies, taking into account how any benefit is balanced against possible risks.

2. Screening for FNAIT

2.1 Screening – does it make sense?

Severe FNAIT (with platelets less than 25 × 10^9/l) occurs in 1 in 10 000 live births; 20% of these have an ICH, up to 80% of which occur during pregnancy rather than in the neonate (14% before 20 weeks of gestation and a further 30% before 30 weeks of gestation). It is clear that the first pregnancy may
be affected by FNAIT and that the diagnosis is often only made after fetal or neonatal bleeding, or a chance finding of thrombocytopenia.

The aim of screening pregnant women for FNAIT would be to detect the condition during the mother’s first affected pregnancy, and to reduce the risk of ICH or intrauterine death for that baby and subsequent babies. The benefits of screening would need to outweigh the risks. Screening would be for FNAIT due to anti-HPA-1a only, as it is the most common antibody and causes 95% of severe FNAIT (with platelets less than 50 × 10^9/l).8,10

In 2012, the UK National Screening Committee concluded that there is not yet convincing evidence of clinical benefits from screening and that it could potentially cause harm through substantial overdiagnosis of FNAIT, prompting intervention. This evidence remains unchanged in their latest review11 of screening for FNAIT on the basis that:

- FNAIT does not harm all babies and there is no test which can tell which babies will be harmed.
- There is no known medical treatment that can prevent FNAIT.
- There is no clear evidence to suggest that screening and subsequent treatment would be better than treating women and babies when problems first arise.

The screening test options reviewed11,12 included genotyping and anti-HPA antibody detection, which are discussed below.

Genotyping
High-throughput, low-cost HPA-1a genotyping is now available. For women identified as HPA-1a-negative, the HPA antigen status of the fetus can be determined from fetal DNA in maternal plasma and if the fetus is HPA-1a negative, no further follow-up is necessary. However, this has not yet been developed as a routine laboratory test.12 Scheffer et al.13 reported 100% sensitivity and 100% specificity for this test in 34 pregnancies in the Netherlands. Alternatively, the father’s HPA-1a genotype can be tested: if negative, no follow-up is required.

Following a positive result from HPA-1a genotyping, further testing for the presence of the human leucocyte antigen (HLA)-DRB3*0101 in women is associated with clinically significant FNAIT,1,14 but a negative predictive value of 99% could be useful to exclude DRB3*0101-negative women from further follow-up. However, such use of this test has not been proven in a large study.

Anti-HPA antibody detection
Low-cost, high-throughput serological methods are available; although some antibodies may be missed.15 Antibodies detected before 20 weeks of gestation may be transient and of no clinical significance. Therefore, antibody testing would need to be repeated later in pregnancy.1 In one Scottish study16 of 19,000 women screened for HPA-1a-negative status and anti-HPA-1a antibodies, where no intravenous immunoglobulin (IVIg) therapy was given, 25/318 HPA-negative women had anti-HPA-1a antibodies; five neonates of these women had severe thrombocytopenia (with platelets less than 50 × 10^9/l) and three had mild bleeding. However, no ICH occurred in the study population. There is some evidence that cases of FNAIT are underreported: from screening studies,1,10,16,17 among the 700,000 births per year in the UK, approximately 1400 would be expected to have maternal anti-HPA antibodies each year and two would have severe fetal thrombocytopenia. However, Knight et al.18 estimated the incidence of clinically-detected FNAIT in the UK as only 12.4 (95% CI 10.7–14.3) per 100,000 births (or 1.2 per 10,000 births); approximately 85 babies per year. There is, therefore, a discrepancy between the estimated numbers of severe FNAIT cases that could be potentially prevented by screening and the numbers of clinically reported FNAIT cases annually (approximately
To avoid overdiagnosis of FNAIT which requires intervention through screening, a reliable test to predict severe clinical disease is desirable. Some studies have suggested that maternal HPA-1a antibody level or titre are predictive, but other studies refute this.

Postnatal screening of all neonates for platelet counts at birth has been advocated, but would not prevent the majority of ICH that occurs antenatally.

The optimal management of FNAIT found on antenatal screening without a prior history is not clear. The benefits of giving mothers IVIg or corticosteroids is derived from their use in subsequent affected pregnancies after diagnosis, as only three cases of treatment of FNAIT identified through screening are published. Of note, although accepted as first-line treatment for subsequently affected pregnancies, the evidence for the prevention of ICH by IVIg is mixed: some studies report good results, while others report failure of IVIg to prevent haemorrhage in severely affected fetuses.

Several authors have suggested that screening might be cost-effective if cases of ICH and their associated costs were prevented.

3. Testing for fetal HPA genotype

Paternal HPA testing is recommended. If the father is heterozygous for the corresponding HPA antigen against which the mother has an antibody, then there are two possible approaches outlined below.

3.1 Invasive testing

An amniocentesis at around 16 weeks of gestation for fetal HPA antigen status can be considered. However, there is a procedure-related 0.5–1.0% risk of miscarriage and possibility of stimulating HPA antibody production. Although fetal platelet antigen genotyping for the most common antigen (HPA-1a) by cell-free DNA testing has been reported, the technique is not established widely as a routine clinical service. If the mother declines amniocentesis, IVIg may be offered empirically from 18 weeks of gestation.

Amniocentesis should define the fetal HPA antigen status, but is also useful to determine the RhD status if the fetus is female. This is important as they should receive rare HPA-1a and -5b-negative platelets, which are also RhD negative, in case the female fetus or neonate is RhD negative.

If amniocentesis is not performed, but the mother is RhD negative, then maternal blood for fetal RhD genotyping should be sent to prevent sensitisation from the administration of RhD-positive platelets to an RhD-negative female baby. If the mother is RhD positive, then maternal blood for fetal RhD genotyping cannot be done. Should RhD-negative platelets not be available for a female neonate as the preferred choice, then RhD-positive platelets must be given without delay. However, before administering anti-D immunoglobulin cover to prevent anti-D sensitisation in the baby, cord blood should be tested and only if the baby is RhD negative should anti-D be administered (subcutaneously rather than intramuscularly, because of the neonate’s low blood count).

3.2 Noninvasive maternal testing for fetal HPA genotype

Noninvasive fetal HPA testing is desirable when it is not clear whether a fetus has the corresponding HPA antigen, against which the mother has an HPA antibody (e.g. if the father is heterozygous for the
HPA antigen, which occurs in approximately 30% of cases; if the biological father is unavailable for testing; or in the setting of donor gamete in vitro fertilisation). Without such testing, potentially unnecessary maternal IVIg is given weekly from 16–18 weeks of gestation until delivery, FBS is undertaken or invasive methods of fetal HPA testing are used, for example, amniocentesis, with the small associated risk of miscarriage.

In 2011, a maternal blood test to allow HPA genotyping on cell-free fetal DNA present in the maternal plasma was reported.13 The study demonstrated in 34 pregnant women that maternal blood could reliably be tested early in the second trimester; before that, false-negative results may occur due to low fetal DNA levels. Nonspecific amplification of maternal (HPA-1b instead of HPA-1a) DNA was mainly overcome by pre-polymerase chain reaction (PCR) digestion of HPA-1a, but occasionally incomplete digestion of maternal HPA-1b DNA can give false-positive or inconclusive fetal results.

In 2013, two further HPA genotyping techniques were reported,29 which were less prone to this problem and which could test for fetal HPA-1a or -1b genes:

- An allele-specific real-time PCR assay using SYBR® Green (Thermo Fisher Scientific, Waltham, MA, USA) technology gave reliable results on samples taken from 49 women, when taken after 17 weeks of gestation, as some discrepancies were seen before that. The technique distinguishes specific from nonspecific amplification of the opposite allele.
- High resolution melting technology on PCR amplicons is based on the difference in melting temperature by 0.7°C of HPA-1a and -1b. Correct results were obtained on all 46 women tested. These techniques appear more specific than the Msp1 restriction method, but still rely on sufficient cell-free fetal DNA being extracted from maternal blood to avoid false-negative fetal results. Controls to ensure that fetal DNA is present also remain a problem. Authors therefore recommend that from 15 weeks of gestation onwards, both tests are used to ensure correct results, notwithstanding the extra costs. However, neither these nor the Msp1 restriction method of testing have been widely adopted in other countries (European or worldwide), reflecting the large resources required to set up and validate tests, and the small numbers of cases involved.

4. Gestation at which to start IVIg

IVIg should be offered to women whose pregnancies are at risk of FNAIT. There are no randomised controlled trials: all evidence is based on case series. Following one pregnancy affected by FNAIT, in the next pregnancy maternal IVIg would normally be first-line therapy. In normal circumstances, it is recommended that IVIg is started at 1 g/kg/week at 18 weeks of gestation.30,31 Where there is a history of a most severely affected sibling (with antenatal ICH or platelets less than 20 × 10^9/l), some authors32 have recommended starting at 12 weeks of gestation. Although there is no clinical evidence, it can be presumed that as it is theoretically before the earliest expression of fetal HPA antigens, the HPA antibody is able to cross the placenta to interact with the antigens.32

Confirmation that the fetus has the corresponding HPA antigen to which the mother has an antibody is desirable. However, unless the father is homozygous for the antigen, fetal HPA genotyping could be done if chorionic villus sampling (after 11 weeks of gestation) or amniocentesis (after 16 weeks of gestation) are carried out for other indications, or in some counties, maternal blood for fetal HPA genotyping is available for HPA-1a or -1b. If unavailable, IVIg may be started ‘blind’.

Some groups advocate different starting times for IVIg depending on the level of risk of severe FNAIT (see Table 1): here a fetus is deemed high risk if a previous baby had an ICH or platelets were less than 20 × 10^9/l.33 Bussel et al.5 treated women according to stratified risk: very high risk (mothers with a previous baby with an ICH and low platelets); extremely high risk (mothers with a previous baby with
Taking such risk stratification into account, Pacheco et al.\(^4\) recommended giving high risk mothers (defined as a previous baby with an ICH and low platelets) IVIg 1 g/kg/week from 12 weeks of gestation, doubling the IVIg or adding in prednisolone empirically at 20 weeks of gestation, and then adding in the other modality from 28 weeks of gestation. However, for those very high risk mothers, whose previous baby had an ICH before 28 weeks of gestation, the treatment recommended is even more intensive: IVIg 2 g/kg/week from 12 weeks of gestation and adding prednisolone from 20 weeks of gestation.

Standard risk mothers (with a previous baby with low platelet count but no ICH) start IVIg 1 g/kg/week plus prednisolone or IVIg 2 g/kg/week at 20 weeks of gestation, then add the other modality at 32 weeks of gestation empirically. All mothers are offered elective caesarean section at 37–38 weeks of gestation. The authors had evidence for using the risk stratification, but none for the intensity of treatment. However, it was advocated to assure maximal treatment in order to avoid the risks of miscarriage or other fetal complications associated with FBS.

In mothers with a previous baby with an ICH, many other groups start IVIg at 16 weeks of gestation\(^31\) or 16–18 weeks of gestation\(^7\) on the basis that fetal platelet antigens are fully expressed by 16–18 weeks of gestation.\(^34\) However, in mothers who have not had a baby with an ICH, these groups do not start IVIg until 28 weeks of gestation\(^7\) or 28–34 weeks of gestation.\(^31\) Many groups prefer to start IVIg earlier, at around 20 weeks of gestation in standard-risk mothers.\(^33\)

5. Is there a role for FBS?

Over the past 10 years, management of FNAIT has moved away from invasive treatment to maternal IVIg as first-line therapy because of the associated risks to the fetus from weekly platelet intrauterine transfusions and FBS, estimated as 6% overall from several studies.\(^30,33,35,36\) However, controversy remains over the role of FBS for assessing the response to IVIg. The concern is that omitting the FBS (usually performed around 6–8 weeks after starting IVIg), the opportunity for identifying nonresponders and adding steroids or doubling the dose of IVIg, or if necessary, giving weekly platelet intrauterine transfusions in order to reduce the risk of ICH, is lost. Some argue that the risks of FBS (once, or repeated before delivery) outweigh the benefits of assessing response to adjust the treatment, so omit FBS altogether.\(^37\) Therefore, FBS is not recommended routinely in standard risk pregnancies but may have a place for high risk women with a previous history of fetal or neonatal ICH,\(^38\) or platelets less than 10 × 10⁹/l at birth.

Van den Akker et al.\(^37\) reported good outcomes in ten neonates born with platelets less than 50 × 10⁹/l; four of whom had a sibling with an ICH. In a further 25 cases with platelets less than 50 × 10⁹/l at birth, two had an ICH, but these occurred before IVIg was started at 28 weeks of gestation.\(^39\) It will be important to collect further data on the outcomes of babies with platelets less than 50 × 10⁹/l, who have been managed with maternal IVIg 1 g/kg/week and no FBS, to ensure the safety of such an approach universally. At present, centres vary in the use of FBS at all and also whether one or more than one FBS procedure is undertaken.

6. Evidence for steroids or escalation of dose of IVIg
The role of steroids is controversial. As a first-line alternative to maternal IVIg, steroids do not reliably raise fetal platelet counts. Furthermore, one study reported no benefit of adding dexamethasone in cases in which no rise in platelet count had been obtained using IVIg 1 g/kg/week alone, but noted significant adverse effects in mothers and in another study, fetal oligohydramnios. Prednisolone has been used without causing oligohydramnios and with fewer maternal adverse effects, although these remain common. Several series using steroids in addition to IVIg have been reported, but numbers in these are limited (Table 1). In one randomised controlled study, mothers with a previous baby with an ICH were excluded, but other mothers had a baseline FBS and were separated into those with fetal platelets less than $20 \times 10^9/l$ (high risk) and those with fetal platelets more than $20 \times 10^9/l$ (standard risk). In the high risk pregnancies, giving prednisolone 1 mg/kg/day in addition to IVIg 1 g/kg/week showed some benefit; with a satisfactory increase in fetal platelet count in 82% of cases compared with only 18% on IVIg alone. However, in standard risk pregnancies, there was no benefit from the addition of steroids to IVIg. In mothers who had a previous baby with ICH due to FNAIT, a trend towards higher platelet counts was found in those given double-dose IVIg 2 g/kg/week or IVIg 1 g/kg/week plus prednisolone. Therefore, in the absence of sufficiently large randomised controlled trials to achieve definitive evidence-based optimal treatment strategies, either treatment may be considered as an option in high risk cases where escalation of treatment is desirable. Selection may also depend on maternal adverse effects associated with steroids (e.g. psychosis, diabetes, hypertension) and IVIg (e.g. severe allergy).
Table 1. Treatment of FNAIT according to stratified risk

<table>
<thead>
<tr>
<th>Reference</th>
<th>Previous pregnancy low platelets</th>
<th>Previous pregnancy with ICH</th>
<th>ICH gestation &lt; 28 weeks of gestation</th>
<th>ICH gestation &gt; 28 weeks of gestation</th>
<th>Treatment advised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bussel, 2010(^5)</td>
<td>&lt; 20 \times 10^9/l</td>
<td>✓</td>
<td></td>
<td></td>
<td>If both, from 12 weeks of gestation, give IVIg 1 g/kg/week +/- prednisolone After FBS at 20–24 weeks of gestation, give IVIg 1 g/kg/week</td>
</tr>
<tr>
<td></td>
<td>✓</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacheco, 2011(^4)</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>From 12 weeks of gestation, give IVIg 1 g/kg/week; double dose or add prednisolone at 20 weeks of gestation; then add other modality from 28 weeks of gestation From 12 weeks of gestation, give IVIg 2 g/kg/week; add prednisolone at 20 weeks of gestation From 20 weeks of gestation, give IVIg 1 g/kg/week and prednisolone; or IVIg 2 g/kg/week; then add other modality at 32 weeks of gestation</td>
</tr>
<tr>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>✓</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kamphuis, 2011(^7)</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>16–18 weeks of gestation, give IVIg 1 g/kg/week</td>
</tr>
<tr>
<td></td>
<td>✓</td>
<td>No</td>
<td></td>
<td></td>
<td>28 weeks of gestation, give IVIg 1 g/kg/week</td>
</tr>
<tr>
<td>Berkowitz, 2006(^3)</td>
<td>✓</td>
<td>No</td>
<td></td>
<td></td>
<td>20 weeks of gestation, give IVIg 1 g/kg/week</td>
</tr>
</tbody>
</table>
7. Future prophylaxis

Currently, two potentially promising approaches to reduce the burden of disease due to FNAIT are being examined, but much more work is still needed before the logistics, risk benefits and cost-effectiveness of each is fully understood.

7.1 PROFNAIT

In the same way that anti-D prophylaxis is given to RhD-negative pregnant women to prevent the forming of immune anti-D antibodies during pregnancy with an RhD-positive fetus, research is underway on a product to prevent women forming immune anti-HPA-1a antibodies.41 The PROFNAIT project42 is a consortium of 11 Northern European hospitals, universities, blood services and companies with expertise in FNAIT, supported by European Union funding from 2012–16, to develop an anti-HPA-1a immunoglobulin for prophylaxis. PROFNAIT received orphan drug status by the European Medicines Agency in 2011 and the Food and Drug Administration in 2013. Phase I and II studies have been completed and a phase III trial is awaited.

7.2 Recombinant HPA-1a antibody to treat FNAIT

Ghevaert et al.43 developed a therapeutic human recombinant high-affinity HPA-1a antibody (B2G1anab) which competes with maternal anti-HPA-1a antibody for binding to fetal HPA-1a-positive platelets. The therapeutic antibody, however, has a modified Fc region which cannot bind with Fcy receptors, so cannot cause FNAIT. Platelets sensitised with both maternal and therapeutic antibodies lasted three times as long in circulation, which, theoretically, could contribute to maintaining fetal platelets more than 20–30 × 10^9/l, reducing the risk of ICH. Further pharmacodynamics and clinical studies on safety, efficacy and dosage are needed. The authors have also suggested that the efficient clearance of platelets sensitised with B2G1 in this study43 might also indicate the potential of B2G1 to be used as an agent for prophylaxis to prevent alloimmunisation in HPA-1a-negative women of childbearing age.

8. Guidance for ultrasound scanning

After scans at 18 and 20 weeks of gestation, serial ultrasound assessments are recommended 2–4 times weekly with a focus on the fetal brain. In reality, the benefit is largely for maternal reassurance in finding no ICH, a reassurance that should not be underestimated. Some authors maintain there is the potential benefit of delivering promptly and treating early if ICH is diagnosed, but prompt treatment is unlikely to be feasible. In case of ICH at an early gestational age, IVIg treatment and prolonging the pregnancy may be considered.

9. Caesarean or vaginal delivery?

The prevalent approach for delivery is a precautionary one in that elective caesarean section at 37 weeks of gestation is the preferred mode of delivery with a course (two doses) of steroids prior to caesarean section (indicated for lung maturity rather than to boost the fetal platelet count). Where a woman is multiparous, induction of labour at 38 weeks of gestation with avoidance of rotational or ventouse delivery, or fetal scalp blood sampling in labour is a reasonable alternative. The evidence to help guide advice regarding mode of delivery is weak.

Elective caesarean section at 36–38 weeks of gestation for all women with anti-HPA-1a antibodies, together with HPA-1a-negative platelet donors for the neonate if petechiae are present and/or the platelet count is less than 35 × 10^9/l has also been suggested,3 in order to reduce trauma, reduce
exposure to HPA-1a antibodies at the end of pregnancy and procure HPA-1a-negative platelets at a specified time. The interpretation of results between intervention and control groups was problematic. A randomised controlled trial of IVIg or preterm caesarean section for FNAIT may not be feasible, as it would be difficult not to treat women whose fetus might be considered at risk of ICH. However, Norway, Denmark and the Netherlands all have different national guidelines for the antenatal management of FNAIT: offering preterm caesarean section, IVIg and cord blood testing only for thrombocytopenia, respectively, which may provide information on each treatment modality in due course.

10. ICH and long-term outcome

Should fetal ICH occur, then management is based on fetal medicine considerations and parental wishes and this is beyond the scope of this document. Long-term outcome data on babies born with an ICH is limited: in one centre in the Netherlands with 20 cases, 50% did not survive and of the survivors, 70% had neurodevelopmental impairments. 44

11. Opinion

- There is no evidence to support routine screening for pregnancies at risk of FNAIT.
- Noninvasive testing in high risk pregnancies is not routinely available as a clinical test in the UK.
- Prophylaxis of the condition remains limited to early phase studies and is not available for clinical use at present.
- The changing pattern of disease following the widespread use of noninvasive therapy with IVIg favours this treatment as opposed to FBS and platelet transfusion in pregnant women with all but the most serious previous pregnancy outcomes.
- IVIg is a safe and effective treatment and in most cases can be started at 16–18 weeks of gestation in an at-risk pregnancy.
- There is little evidence for the role of IVIg from 12 weeks of gestation and/or addition of steroids.

References


42. PROFNAIT Project [http://www.profnait.eu/profnait-project/project-funding/].


44. D Oepkes, personal communication.
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