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

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Plain language summary

What is it?

Fetal neonatal alloimmune thrombocytopenia (FNAIT), also known as neonatal alloimmune thrombocytopenia (NAIT) or fetomaternal alloimmune thrombocytopenia (FMAIT), is a rare condition which affects a baby's platelets. This can put them at risk of problems with bleeding, particularly into the brain. One baby per week in the UK may be seriously affected and milder forms can affect one in every 1000 births.

How is it caused?

Platelets are blood cells that are very important in helping blood to clot. All platelets have natural proteins on their surface called human platelet antigens (HPAs). In babies, half of these antigens are inherited from the mother and half from the father. During pregnancy, some of the baby's platelets can cross into the mother's bloodstream. In most cases, this does not cause a problem. But in cases of FNAIT, the mother's immune system does not recognise the baby's HPAs that were inherited from the father and develops antibodies, which can cross the placenta and attack the baby's platelets. These antibodies are called anti-HPAs, and the commonest antibody implicated is anti-HPA-1a, but there are other rarer antibody types. If this happens, the baby's platelets may be destroyed causing their platelet count to fall dangerously low. If the platelet count is very low there is a risk to the baby of bleeding into their brain before they are born. This is very rare but if it happens it can have serious effects on the baby's health.

How is it inherited?

A baby inherits half of their HPAs from its mother and half from its father. Consequently, a baby may have different HPAs from its mother. As the condition is very rare, and even if the baby is at risk of the condition we have no way of knowing how severely they will be affected, routine screening is not currently recommended.

What can be done?

FNAIT is usually diagnosed if a previous baby has had a low platelet count. The parents are offered blood tests and the condition can be confirmed or ruled out. There are many other causes of low platelets in babies, which may also need to be tested for. As the condition is so rare, expertise is limited to specialist centres and normally a haematologist and fetal medicine doctor will perform and interpret the tests together. Fortunately, there is an effective treatment for the vast majority of cases called immunoglobulin, or IVIg. This 'blood product' is given intravenously through a drip every week to women at risk of the condition. It may be started from as early as 16 weeks in the next pregnancy, until birth, which would be offered at around 36–37 weeks. Less common treatments that may be considered depending on individual circumstances include steroid tablets or injections, or giving platelet transfusions to the baby.

What does this paper tell you?
This paper considers the latest evidence in relation to treatment options in the management of pregnancies at risk of FNAIT. Specifically, we discuss the role of screening, when IVIg should be started, what dose should be used, and what evidence there is for maternal steroids. We also consider in very rare selected cases, the use of fetal blood sampling and giving platelet transfusions to the baby before birth. Finally, we consider the approaches to blood testing mothers to tell if babies are at risk, which is offered in some countries, and development of new treatments to reduce the risk of 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 that occurs in a first pregnancy may not be diagnosed until the neonatal period. The incidence of FNAIT is approximately 1 in 1000 pregnancies.[1–3] 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.[4,5] Rarely, FNAIT is detected de novo where an ultrasound scan detects ventriculomegaly; in these situations a maternal FNAIT antibody screen is frequently undertaken.

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.[6] 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,[7] 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. Severe FNAIT is very rare, adverse consequences for the fetus are potentially disastrous and the treatments are costly. 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. In addition, the question whether scientific

research has shown treatments to be of benefit to women and their babies is discussed, taking into account how any benefit is balanced against possible risks.

2. Screening for FNAIT

Severe FNAIT (defined by the study authors as platelets less than 25 $\times$ 10^9/l) occurs in 1 in 10 000 live births;[8] up to 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).[9] It is clear that the first pregnancy may be affected by FNAIT and that the diagnosis is made only 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 solely for FNAIT due to anti-HPA-1a, as it is the most common antibody and causes 95% of severe FNAIT (defined by the study authors as platelets less than 50 $\times$ 10^9/l).[8,10]

In 2012, the UK National Screening Committee concluded that there was not yet convincing evidence of clinical benefits from screening and that it could potentially cause harm through substantial overdiagnosis of FNAIT, prompting intervention. This recommendation remains unchanged in their 2017 review[11] 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 reviewed[11,12] include genotyping and anti-HPA detection, which are discussed below.

2.1 Genotyping

High-throughput, low-cost HPA-1a genotyping is now available. For women identified as HPA-1a-negative, the HPA 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 and if negative, no follow-up is required.

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

2.2 Anti-HPA 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. Antibody testing would

therefore need to be repeated later in pregnancy.[1] In one Scottish study[2] of 19 000 women screened for HPA-1a-negative status and anti-HPA-1a, where no intravenous immunoglobulin (IVIg) therapy was given, 25/318 HPA-negative women had anti-HPA-1a; 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 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 potentially be prevented by screening and the numbers of clinically reported FNAIT cases annually (approximately 14%). In addition, 30% of FNAIT cases occur in pregnancies with a previous sibling history of FNAIT. As a result, screening would be of no benefit in the current pregnancy.[18]

To avoid overdiagnosis of FNAIT which requires intervention through screening, a reliable test to predict severe clinical disease is desirable. Small cohort studies suggest that maternal anti-HPA-1a level or titre are predictive,[19] but other studies[2,20] contradict 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.[21]

The optimal management of FNAIT found on antenatal screening without a prior history is not clear. The benefits of giving mothers IVIg or corticosteroids derive from their use in subsequent affected pregnancies after diagnosis, as only three cases of treatment of FNAIT identified through screening have been published.[11] 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[22–24] report good results, while others[25–27] report failure of IVIg to prevent haemorrhage in severely affected fetuses.

Several authors[2,28] have suggested that screening might be cost-effective if cases of ICH and their associated costs were prevented.

3. Testing for fetal HPA genotype in the at-risk mother

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

3.1 Invasive testing

An amniocentesis at around 16 weeks of gestation for fetal HPA status can be considered. However, there is a procedure-related 0.5–1.0% risk of miscarriage and possibility of stimulating anti-HPA production. Although fetal platelet antigen genotyping for the most common antigen (HPA-1a) by cell-free DNA (cfDNA) testing has been reported, the technique is not established widely as a routine clinical service.[13,29] If the mother declines amniocentesis, IVIg may be offered empirically from 18 weeks of gestation. This approach, while avoiding the potentially catastrophic consequences of failing to treat, will inevitably lead to unnecessary treatment in 50% of women with its attendant costs and risks of treatment.

Amniocentesis should define the fetal HPA status, but is also useful to determine the rhesus D (RhD) status if the fetus is female. This is important as such women 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. If RhD-negative platelets are not available as the preferred choice for a female neonate, 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, against which the mother has an anti-HPA, for example, if the mother has anti-HPA-1a and the father is heterozygous for HPA-1a, which occurs in approximately 30% of cases. Other examples include situations where the biological father is unavailable for HPA testing; or in the setting of donor gamete in vitro fertilisation, where the donor cannot be HPA tested. In the absence of knowledge on whether the fetus has HPA to which the mother has an anti-HPA, potentially unnecessary maternal IVIg is given weekly from 16–18 weeks of gestation until birth, 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 fetal cfDNA 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 technology (Thermo Fisher Scientific, Waltham, MA, USA) 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 fetal cfDNA being extracted from maternal blood to avoid false-negative fetal results. Controls to ensure that fetal DNA is present also remain a problem. The study therefore recommends that from 15 weeks of gestation onwards, both tests are used in order 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 major 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 (RCTs) comparing IVIg to placebo or invasive management with platelet intrauterine transfusion (IUT): all evidence is based on case series.[30] Following one pregnancy affected by FNAIT, maternal IVIg would normally be first-line therapy in the next pregnancy at 1 g/kg/week from 18 weeks of gestation.[31,32] Where there is a history of a most severely affected sibling (with antenatal ICH or platelets less than 20×10^9/l), some authors[33] have recommended starting at 12 weeks of gestation. Although there is no clinical evidence for this, it can be presumed that as it is theoretically before the earliest expression of fetal HPAs, the HPA antibody is able to cross the placenta to interact with the antigens.[33]

Confirmation that the fetus has the corresponding HPA 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 countries, 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[4,5] (see Appendix I): here a fetus is deemed high risk if a previous baby had an ICH or platelets were less than 20×10^9/l.[34] 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 low platelets and an ICH which occurred before 28 weeks of gestation); and high risk (mothers with a previous baby with low platelets but no ICH). Extremely high risk and very high risk patients received IVIg 1 g/kg/week with or without prednisolone from 12 weeks of gestation and had an FBS at 20–24 weeks of gestation. High risk patients had IVIg only after an FBS at 20–24 weeks of gestation. The authors concluded that with risk stratification, the ICH rate was very low (5/37 fetuses, two of which were not due to thrombocytopenia).

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[32] or 16–18 weeks of gestation[7] on the basis that fetal platelet antigens are fully expressed by 16–18 weeks of gestation.[35] 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.[32] Many groups prefer to start IVIg earlier, at around 20 weeks of gestation in standard-risk mothers.[34]

5. Is there a role for FBS by cordocentesis?

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 IUTs and FBS, estimated as 6% overall from several studies.[31,34,36,37] However, controversy remains over the role of FBS for assessing the response to IVIg. The concern is that by omitting the FBS (usually performed around 6–8 weeks after starting IVIg), the opportunity for identifying non-responders and adding steroids or doubling the dose of IVIg, or if necessary, giving weekly platelet IUTs in order to reduce the risk of ICH, is lost. One group[38] argues that the risks of FBS (once, or repeated before delivery) outweigh the benefits of assessing the response in order to adjust the treatment, and omit FBS altogether. FBS is not therefore recommended routinely in standard risk pregnancies but may have a place for high risk women with a previous history of fetal or neonatal ICH,[39] or platelets less than 10×10^9/l at birth.

Van den Akker et al.[38] reported good outcomes in ten neonates born with platelets less than 50×10^9/l; four of whom had a sibling with an ICH. In a further 25 cases with platelets less than 50×10^9/l at birth, two had an ICH, but these occurred before IVIg was started at 28 weeks of gestation.[40] It will be important to collect further data on the outcomes of babies with platelets less than 50×10^9/l, who have been managed with maternal IVIg 1 g/kg/week and no FBS, to ensure the safety of such an approach universally. Centres vary in whether they use FBS at all and 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.[41] Furthermore, one study[23] 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,[22] oligohydramnios in the fetus. Prednisolone has been used without causing oligohydramnios and with fewer maternal adverse effects, although these remain common.[8] Several series using steroids in addition to IVIg have been reported,[4,5] but numbers in these are limited (Appendix I). In one randomised controlled study,[34] 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 20×10^9/l (high risk) and those with fetal platelets more than 20×10^9/l (standard risk). In the high risk pregnancies, administration of 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.[8] Therefore, in the absence of sufficiently large RCTs 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).

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 formation 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.[42] The PROFNAIT project[43] is a consortium of 11 Northern European hospitals, universities, blood services and companies with expertise in FNAIT, supported by European Union funding from 2012–18, to develop an anti-HPA-1a immunoglobulin for prophylaxis. PROFNAIT received orphan drug status from the European Medicines Agency in 2011 and the Food and Drug Administration in 2013. Phase I and II studies have been completed but have not yet reported and a phase III trial is awaited.

7.2 *Recombinant anti-HPA-1a to treat FNAIT*

Ghevaert et al.[44] developed a therapeutic human recombinant high-affinity anti-HPA-1a (B2G1Δnab) which competes with maternal anti-HPA-1a for binding to fetal HPA-1a-positive platelets. The therapeutic antibody, however, has a modified Fc region which cannot bind with Fcγ receptors, so cannot cause FNAIT. Platelets sensitised with both maternal and therapeutic antibodies lasted three times as long in the circulation, which, theoretically, could contribute to maintaining fetal platelets greater than 20–30 $\times$ 10^9/l, thus 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 study[44] might indicate the potential of B2G1 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 every 2–4 weeks with a focus on the fetal brain. In reality, the benefit is largely in terms of maternal reassurance in finding no ICH, a comfort that should not be underestimated. In case of ICH at an early gestational age, IVIg treatment and prolonging the pregnancy may be considered.

9. Caesarean or vaginal birth?

The prevalent approach for delivery in women whose current pregnancy is at risk of FNAIT and where there has been a previous pregnancy history of FNAIT is a precautionary one. Elective caesarean section at 37 weeks of gestation is the preferred mode of birth 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 birth is weak.

Elective caesarean section at 36–38 weeks of gestation for all women with anti-HPA-1a, together with HPA-1a-negative platelet donors for the neonate if petechiae are present and/or the platelet count is less than 35 $\times$ 10^9/l has also been suggested,[3] in order to reduce trauma, reduce exposure to anti-HPA-1a 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. An RCT 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 which are beyond the scope of this document. Long-term outcome data on babies born with an ICH are limited: in one centre in the Netherlands with 20 cases, 50% did not survive and of the survivors, 70% had neurodevelopmental impairments.[45]

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 associated risks to the fetus from weekly platelet IUTs has led to the widespread introduction of noninvasive IVIg therapy: FBS with platelet transfusion is obsolete as first line therapy.
- IVIg in pregnancy is safe and likely to be effective. It seems reasonable to start therapy at 16–18 weeks of gestation in an at-risk pregnancy.
- There is little evidence for the role of IVIg between 12 and 16 weeks of gestation and/or addition of steroids.

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Appendix I: Treatment of FNAIT according to stratified risk

Reference	Previous pregnancy low platelets	Previous pregnancy with ICH	ICH gestation < 28 weeks of gestation	ICH gestation > 28 weeks of gestation	Treatment advised
Bussel et al.[5]	$< 20 \times 10^9$/l	✓			If both, from 12 weeks of gestation, give IVIg 1 g/kg/week ± prednisolone
	✓	No			After FBS at 20–24 weeks of gestation, give IVIg 1 g/kg/week
Pacheco et al.[4]	✓	✓		✓	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
	✓	No			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
Kamphuis et al.[7]		✓			16–18 weeks of gestation, give IVIg 1 g/kg/week
	✓	No			28 weeks of gestation, give IVIg 1 g/kg/week
Berkowitz et al.[34]	✓	No			20 weeks of gestation, give IVIg 1 g/kg/week

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