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Fetal and neonatal alloimmune thrombocytopenia

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Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is one of the major causes of both severe thrombocytopenia and intracranial haemorrhage in fetuses and term neonates. The incidence of FNAIT is estimated to be one in 1000–2000 births. FNAIT is caused by maternal immunoglobulin G alloantibodies, which cross the placenta and are directed against human platelet antigens (HPA) on fetal platelets. In Caucasian individuals, the immunodominant antigen is HPA-1a, which is responsible for approximately 85% of FNAIT cases. The most feared complication of a low platelet count in the fetus or the neonate is intracranial haemorrhage and subsequent neurological handicaps. Over the last 15 years, there has been a gradual change in antenatal treatment, from an invasive management protocol to a less invasive management protocol to a completely non-invasive approach. However, controversy still exists over the optimal antenatal management strategy.

Key words: alloimmune thrombocytopenia; fetal blood sampling; human platelet antigens; intracranial haemorrhage; intravenous immunoglobulin.

INTRODUCTION

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is one of the major causes of both severe thrombocytopenia and intracranial haemorrhage (ICH) in fetuses and term neonates.^{1,2} The incidence of thrombocytopenia ($<150 \times 10^9/L$) in all newborns is 1–4%; however, due to the absence of clinical signs, it is often not noted.

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Thrombocytopenia with an immunological origin is encountered in 0.3% of the newborns.²⁻⁶ FNAIT and idiopathic thrombocytopenic purpura (ITP) are the most important immune-mediated thrombocytopenias. In this chapter we focus on the FNAIT.

The diagnosis is made (rarely) during pregnancy when ICH occurs as a consequence of severe fetal thrombocytopenia, or within the first days after delivery because of neonatal bleeding manifestation or, most often, because of a coincidental finding of neonatal thrombocytopenia. Therefore, testing for this disorder should be performed for any fetus or neonate with an unexplained ICH and for any neonate with unexplained thrombocytopenia, with and without bleeding symptoms, both for proper treatment as for future pregnancies.

FNAIT is caused by maternal immunoglobulin G (IgG) alloantibodies, which cross the placenta and are directed against human platelet antigens (HPA) on fetal platelets. The mechanism is the platelet equivalent of Rhesus disease but, unlike Rhesus disease, it can occur in a severe form in the first pregnancy. As routine screening programs for HPA antibodies is not (yet) done, it invariably occurs unexpectedly. Like Rhesus disease, FNAIT seems to worsen in subsequent pregnancies.^{3,7,8}

INCIDENCE, NATURAL HISTORY AND PATHOPHYSIOLOGY

FNAIT occurs in approximately 1:1500 random fetuses/newborns.⁹⁻¹⁵ It is the result of an immunological process in which the mother produces an antibody-mediated response against a platelet-specific antigen that she herself lacks but that is present on the fetal platelets, inherited from the father. The specific HPAs identified so far are

Table 1. Human platelet antigens 16.

System	Antigen	Original names	Glycoprotein	Nucleotide change	Amino acid change	CD
HPA-1	HPA-1a	Zwa, PIA1	GP1IIa	T176	Leu33	CD61
	HPA-1b	Zwb, PIA2		C176	Pro33	
HPA-2	HPA-2a	Kob	GP1b α	C482	Thr145	CD42b
	HPA-2b	Koa, Siba		T482	Met145	
HPA-3	HPA-3a	Baka, Leka	GP1Ib	T2621	Ile843	CD41
	HPA-3b	Bakb		G2621	Ser843	
HPA-4	HPA-4a	Yukb, Pena	GP1IIa	G506	Arg143	CD61
	HPA-4b	Yuka, Penb		A506	Gln143	
HPA-5	HPA-5a	Brb, Zavb	GP1a	G1600	Glu505	CD49b
	HPA-5b	Bra, Zava, Hca		A1600	Lys505	
	HPA-6bw	Caa, Tua	GP1IIa	1544G > A	Gln489Arg	CD61
	HPA-7bw	Moa	GP1IIa	1297C > G	Ala407Pro	CD61
	HPA-8bw	Sra	GP1IIa	1984C > T	Cys636Arg	CD61
	HPA-9bw	Maxa	GP1Ib	2602G > A	Met837Val	CD41
	HPA-10bw	Laa	GP1IIa	263G > A	Gln62Arg	CD61
	HPA-11bw	Groa	GP1IIa	1976G > A	His633Arg	CD61
	HPA-12bw	Iya	GP1b β	119G > A	Glu15Gly	CD42c
	HPA-13bw	Sita	GP1a	2483C > T	Met799Thr	CD49b
	HPA-14bw	Oea	GP1IIa	1909_1911 Del AAG	Del Lys611	CD61
HPA-15	HPA-15a	Govb	CD109	C2108	Ser703	CD109
	HPA-15b	Gova		A2108	Tyr703	
	HPA-16bw	Duva	GP1IIa	497C > T	Thr140Ile	CD61

all known to be able to cause FNAIT and are shown in Table 1. This table lists also the glycoproteins (GP) on which the antigens are located, the position of the genetic single nucleotide polymorphism and the amino acid change.¹⁶

The immunodominant antigen in Caucasian individuals is the HPA-1a, which is responsible for approximately 85% of FNAIT cases.^{17,18} Two per cent of pregnant Caucasian women are HPA-1a negative.^{11,13,19,20} The proportion of individuals belonging to a particular platelet antigen type varies according to the race involved. Some of these differences in frequencies of HPA alloantigens in different populations are shown in Table 2.^{21–26}

Untreated newborns with FNAIT are reported to be affected by ICH in 7–26% of cases.^{17,18,27–33} There is surprisingly little information about both the pathophysiology and natural history of FNAIT. FNAIT is considered the platelet equivalent of red cell alloimmunisation or haemolytic disease of the newborn. However, in contrast to red cell alloimmunisation, FNAIT occurs in the first pregnancy in over 50% of cases.¹⁷

HPA antigens are already expressed on fetal platelets in the first trimester. Once the mother has produced HPA antibodies, these specific IgG antibodies are able to cross the placenta and cause platelet destruction in the fetus. Unfortunately, there is a lack of a reliable, clinically useful correlation between the maternal antibody levels and the severity of FNAIT^{34–36}, although some studies showed a higher risk of severe FNAIT with high antibody levels.^{37,38}

Although thrombocytopenia is commonly defined as a platelet count below $150 \times 10^9/L$, clinical symptoms are only likely to occur when the platelet count drops to below $50 \times 10^9/L$.³⁹ The most feared complication of a low platelet count in the fetus or the neonate is ICH, with its subsequent neurological handicaps. In a literature review by Spencer and Burrows, ICH was reported to occur in 74/281 (26%) of cases of FNAIT.¹⁸ Mortality related to ICH is estimated to occur in 7% of cases.^{18,31} In a study by Bussel et al an incidence of ICH of 11% was found in a series of 110 cases of FNAIT.¹

ANALYSIS IN THE NEXT PREGNANCY

Maternal–fetal HPA incompatibility has to be confirmed for all patients by paternal HPA typing. In cases where the father is homozygous for the specific HPA antigen,

Table 2. Human platelet alloantigen frequencies.

Antigens	Percentage frequency						
	Caucasian	Japanese	Korean	African-American	Indian	Indonesian	Han Chinese
HPA-1a	97.9	>99.9	99.5	99.9	99.9	>99.4	>99.9
HPA-1b	28.6	3.7	2.0	16.0	n.t.	n.t.	1.2
HPA-2a	>99.9	n.t.	99.0	97.0	n.t.	n.t.	99.9
HPA-2b	13.2	25.4	14.0	33.0	n.t.	n.t.	9.6
HPA-3a	80.9	78.9	82.5	85.0	89.3	72.9	83.1
HPA-3b	69.8	70.7	71.5	60.0	n.t.	80.7	64.2
HPA-4a	>99.9	99.9	>99.9	100.0	99.9	>99.4	>99.9
HPA-4b	0.0	1.7	2.0	0.0	0.9	0.6	0.9
HPA-5a	99.0	n.t.	>99.9	96.0	n.t.	>99.4	99.9
HPA-5b	19.7	n.t.	4.5	38.0	4.9	9.3	2.7

n.t., not tested.

one can assume that the fetus is at risk. In cases where the father is heterozygous for the HPA antigen, amniocentesis is currently used for fetal HPA typing. Methods are being developed to assess the fetal HPA-type using free fetal DNA in maternal plasma. Unfortunately, quantifying and serial monitoring anti-HPA antibodies does not accurately predict the severity of fetal thrombocytopenia.^{34,35,38}

Therefore, all pregnancies in which the mother carries HPA antibodies and the fetus is positive for the corresponding HPA antigen must be regarded as at risk for low fetal and neonatal platelet counts and bleeding complications. The only distinction made in the at-risk group is based on whether the previous affected child had asymptomatic low platelet counts or suffered from actual bleeding problems especially ICH. The latter group is regarded as a higher-risk group although, as stated before, very little is known about the natural history.

ANTENATAL TREATMENT

As most countries do not have a screening program, women are identified as at risk only after a previous child with FNAIT. The goal of antenatal treatment is to prevent severe thrombocytopenia and the concomitant risk for ICH and its sequelae, including death (which can occur either antenatally or after birth) or severe disability. Several treatment options are available, depending on the severity of the illness of the previous sibling.

Before 1984, the traditional management of subsequent pregnancies in women with a previous history of FNAIT consisted of an early elective caesarean section and transfusion of platelets after birth.

Antenatal treatment: fetal blood sampling and intrauterine platelet transfusion

In 1984, Daffos et al published the successful use of fetal blood sampling (FBS) in obtaining fetal platelet count at 34 weeks, followed by an intrauterine platelet transfusion (IUPT) at 37 weeks, followed by a caesarean section.⁴⁰ Since then, FBS with and without IUPT became standard treatment, in different regimes: from a weekly to only a pre-delivery one. However, although this seemed to be a method to keep platelet counts at a safe level, it became more and more clear that this was a hazardous procedure, especially for fetuses with thrombocytopenia. Based on a review of the literature, the complication rate of FBS and IUPT in FNAIT pregnancies was calculated as 1.6% fetal loss and 2.4% other complications.⁴¹ Data from three recent studies combined showed a 6% fetal loss rate directly related to FBS.⁴²⁻⁴⁴

Antenatal treatment: maternal treatment

Driven by the risks of invasive treatment in FNAIT, maternal treatment was explored. In 1984, Daffos et al reported the successful use of corticosteroids⁴⁰, but in later publications they found that this treatment did not raise fetal platelet count.³¹

Bussel et al.²⁹ were the first to report the effects of maternal administration of intravenous gammaglobulin (IVIG) in the treatment of FNAIT. In all seven cases reported, the fetal platelet count increased substantially after treatment with IVIG 1.0 g/kg/week. Many centres since have adopted this policy. Later studies found that not all fetuses show a substantial increase in platelet count with this treatment. The reported response rate in the literature varies between 30% and 85% (unpublished data). In addition, observational studies have

suggested that IVIG reduced the risk of ICH even in non-responders to IVIG.^{32,45,46} One randomised, placebo-controlled trial was published in 1996 by Bussel et al., in which no effect of adding dexamethasone to the administered IVIG was observed.³²

The mechanism of action of IVIG in FNAIT is still unclear. Three possible explanations are cited in the literature. First, in the maternal circulation the IVIG will dilute the anti-HPA antibodies, resulting in a lower proportion anti-HPA antibodies among the IgG transferred via the Fc-receptors in the placenta. Second, in the placenta, IVIG can block the placenta receptor (Fc-R) and decrease the placental transmission of maternal antibodies including anti-HPA-antibodies. Third, in the fetus, IVIG may block the Fc-receptors on the macrophages and prohibit the destruction of antibody-covered cells.⁴⁷ We found evidence for the first mechanism.⁴⁸ However, other effects of IVIG, such as anti-idiotypic neutralisation of anti-HPA antibodies or suppression of antibody producing B cells, cannot be excluded.

The long-term side-effects for mother and child are still unclear. A recent study on short-term follow-up found a possible increase of IgE in children after maternal IVIG administration compared to the normal population. However, no clinically apparent adverse effects in early childhood could be demonstrated.⁴⁸ As IVIG is known for its immunomodulating characteristics, there are concerns about long-time side effects for the mother and child.

IVIG is widely used in other diseases, such as in prophylaxis and therapy of complications after stem-cell transplantation⁴⁹, autoimmune thrombocytopenic purpura (ITP)⁵⁰ and dermatological and neurological diseases. The dose of 1.0 g/kg/week has been commonly used since Bussel et al.'s first publication.²⁹ In FNAIT, no lower doses of IVIG are published and no dose-effect studies have yet been done. Results of a recent study suggest that placental antibody transfer is not further increased despite high IgG concentrations in the mother as a result of IVIG treatment.⁴⁷ In other immune platelet disorders, the optimal dose of IVIG is also still unclear. For example, in treating ITP, an effective dose of IVIG appears to be between 0.5 and 1.0 g/kg per day, commonly for 5 days.⁵⁰ If no response is observed, increased doses are suggested to a maximum of 2.0 g/kg per day.

The results of a recent study suggest that placental antibody transfer is not further increased despite high IgG concentrations in the mother as a result from IVIG treatment. This suggests a limitation of the placental Fc-receptor.⁴⁷ When maternal titres of anti-HPA antibodies are low, a lower dose of IVIG might be sufficient to reduce transmission of pathogenic HPA-antibodies leading to thrombocytopenia.

Based on the lack of rationale for the dose of 1 g/kg/week, the cost of IVIG and the long-term effects of IVIG on the infants are unknown. An international multicentre study is currently being performed comparing the preventive effect of IVIG 0.5 and 1.0 g/kg/week on FNAIT and ICH in patients with FNAIT and a low risk for ICH. More information can be obtained from the website for the study (www.noich.org).

Antenatal treatment: present situation

Over the last 15 years, there has been a gradual change in antenatal treatment, from an invasive management protocol to a less invasive management protocol to a completely non-invasive approach. However, there is still controversy over the optimal antenatal treatment, especially the safety of the completely non-invasive policy.

The recent study by Berkowitz et al.⁵¹ states that FBS still has a place in treatment with or without platelet transfusion therapy. van den Akker et al have published their

treatment experience over the last 16 years, in which period the transition occurred from an invasive strategy, via a minimally invasive to an ultimately completely non-invasive strategy. The completely non-invasive approach resulted in an excellent outcome for all⁴⁹ non-invasively treated patients, without any loss or complications of FBS.⁵² The non-invasive strategy was supported when these results were compared with two recently published series in which more invasive management protocols were used. Birchall et al. reported on an observational study from 12 European centres, with a total of 50 women with 55 pregnancies and 56 fetuses, all with HPA-Ia alloimmunisation treated between 1988 and 2001.⁴³ Multiple management options were described, all after an initial FBS. ICH occurred in 5% of the children (3/56). FBS-related adverse outcomes occurred in 18% of the fetuses (10/56), with two fetal losses and eight deliveries before 34 weeks' gestation. In addition, in 9% (5/56) an emergency delivery after 34 weeks' gestation had to be performed following FBS. Maternal treatment with IVIG was used in 18 patients, combined with one or more FBSs. Four of these 18 neonates were born before 34 weeks, one fetal loss occurred and one emergency caesarean section was performed, both associated with FBS. The mean platelet count at birth in this group was $80 \times 10^9/L$ with 6 of the 18 neonates having a platelet count $< 50 \times 10^9/L$. None of their cases were treated completely non-invasively.

Berkowitz et al. performed a randomised, multicentre study stratifying 79 pregnancies in a high-risk and a low-risk arm.⁴⁴ All women underwent initial FBS at 20 weeks' gestation. High risk cases ($n = 40$) were defined as either a sibling with peripartum ICH or an initial platelet count $< 20 \times 10^9/L$. Randomisation was between IVIG and prednisone, or IVIG only. Low-risk cases were randomly assigned to IVIG or prednisone. A second FBS was used to adapt the medication dose in non-responders. Platelet transfusions were given in an unknown number of cases. ICH occurred in three cases (4%). Emergency deliveries related to FBS were required in 13% (10/79) of the pregnancies and 24% (19/79) of the neonates were born before 34 weeks. One fetus died due to a complication of FBS; two pregnancies ended in unexplained fetal demise. A total of 175 FBSs were done, with serious complications occurring in 6%. Mean platelet count at birth in the high-risk group was $99 \times 10^9/L$ in the IVIG group and $69 \times 10^9/L$ in the IVIG combined with steroids group. In the low-risk group, 15% (6/39) of fetuses had a platelet count $< 50 \times 10^9/L$.

In Table 3, the LUMC cases (only the non-invasive treated cases) are compared to the IVIG treated cases described by Birchall and those described by Berkowitz. Van den Akker et al concluded that the considerable number of complications and adverse outcomes associated with FBS described by Birchall and Berkowitz could be acceptable if the invasive management would result in a better overall outcome when compared with a completely non-invasive approach. But there seems to be no advantage to the use of FBSs in the management of pregnancies complicated by FNAIT. Adherence to the principle of *primum non nocere* means, in our view, that potentially hazardous diagnostic procedures should be employed only when proven to do more good than harm.⁵²

After cost-effectiveness analysis by Thung et al, which compared non-invasive empiric intravenous immunoglobulin with FBS-based treatment, non-invasive IVIG was found to be a cost-effective strategy when the rate of perinatal ICH is less than 28%.⁵³

DELIVERY

Caesarean section is often routinely employed for delivery in pregnancies with FNAIT. Practice guidelines advise vaginal delivery as an option in case of a platelet

Table 3. Outcomes of antenatal treatment of FNAIT in three different studies.

Sibling	LUMC ^{53,a}		Birchall et al. ^{43 b}		Berkowitz et al. ⁴⁴			
	ICH	No ICH	ICH	No ICH	High risk ^d 7 ICH 33 no ICH		Standard risk ^e No ICH	
Treatment	IVIG n = 5	IVIG n = 48 ^c	IVIG n = 6	IVIG n = 12	IVIG n = 21	IVIG + steroids n = 19	IVIG n = 19	Steroids n = 20
Mean platelet count sibling	20.7 (1 n.a.)	15	7 (5 n.a.)	37.9	28.4	14.4	23	25.7
ICH in sibling	5	0	6	0	4	3	0	0
Mean GA at first treatment	16	32	25	28	24	25	24	25
Delivery mode: vaginal delivery	0/5	31/48 (65%)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Mean platelet count at birth	55.4	137	78.3	82.7	99.4	68.9	n.a.	n.a.
Platelet count $\leq 50 \times 10^9/L$	4/5 (80%)	6/48 (13%)	2/6 (33%)	4/12 (33%)	n.a.	n.a.	6/39 (15%)	
ICH	0	0	1/6 (17%) ^g	0	1	0	2/39 (5%) ^f	
Unexplained fetal demise	0	0	0	0	0	0	1	1
Loss rate due to FBS	0	0	1/6 (17%) ^g	0/12	1/79 (1.3%)			
Emergency delivery due to FBS	0	0	1/6 (17%) ^g	2/12 (17%)	10/79 (13%)			
Delivery before 34 weeks	0	0	4/6 (67%)	0	19/79 (24%)			
Neonatal survival	100%		17/18 (94%)		76/79 (96%)			

FBS, fetal blood sampling; GA, gestational age; ICH, intracerebral haemorrhage; IVIG, intravenous gammaglobulin; LUMC, Leiden University Medical Centre; n.a., not available;

^a Subgroup from total study group, only non-invasive treated cases.

^b Subgroup from total study group, only IVIG treated cases.

^c 48 neonates, resulting from 47 pregnancies.

^d Women in the high-risk arm: either a previous child with a peripartum ICH and/or an initial platelet count $< 20 \times 10^9/L$.

^e Women in the standard risk arm: prior child without ICH and initial platelet counts $> 20 \times 10^9/L$.

^f Possibly not related to FNAIT.

^g Emergency caesarean section at 24 + 2 weeks due to premature labour caused by infection introduced by cordocentesis.

count $> 50 \times 10^9/L$ established by FBS with or without an IUPT.^{8,32,54} Spencer and Burrows estimated that the bleeding occurs (long) before labour in 80% of neonates with ICH.¹⁸ As we estimate the ICH risk to be 7% in a subsequent pregnancy after a previous child with thrombocytopenia but without ICH, this implies that the chance of developing ICH during labour or postpartum is approximately 1.4% in this group. Van den Akker et al did an evaluation on the safety of vaginal delivery in pregnancies with FNAIT by studying 32 pregnancies with FNAIT with a sibling with thrombocytopenia but without an ICH. They found that vaginal delivery was not associated with neonatal intracranial bleeding.⁵⁵

SCREENING

The pros and cons for FNAIT screening have been discussed for several years.^{10,11,15,19,38,56} Williamson et al. showed that 1 in 450 random pregnant women produce HPA-Ia antibodies.¹¹ Based on literature, the incidence of new cases of FNAIT is 1: 1200. Severe FNAIT ($< 50 \times 10^9$ platelets/L) is seen in 1: 1700 random newborns resulting in neonatal ICH in 1: 37,000.⁹⁻¹⁵ Durand-Zaleski et al. compared the costs and clinical outcomes of screening primiparous women with screening all neonates. They found that neonatal screening was the more cost-effective approach.¹⁰ There is no clear approach to antenatal therapy for the first affected pregnancy with FNAIT.¹⁹ However, Davoren et al argue that antenatal screening can identify those fetuses at risk for FNAIT and, even if the optimal antenatal management has not yet been established, high-risk pregnancies can be identified and at least early post-natal treatment can be started.¹³

As well as screening for HPA antibodies in pregnancy, female relatives of affected women could be tested for their HPA status and, if found to be negative for the same HPA type, serial antibody screening during their pregnancies could be done. In addition, these sisters could be tested for HLA-DRw52a. If the affected patient is HLA-DRw52a positive and the female relative is HLA-DRw52a negative, the chance that FNAIT will occur is very low, even if there is a parental antigen mismatch with the relative and her partner.^{57,58}

THE FUTURE

At present, the optimal treatment strategy for pregnancies complicated by FNAIT is still not clear. We hope that it will be possible to abandon the invasive procedures with their inherent risks in the future. As in Rhesus alloimmunisation, in which the diagnosis of fetal anaemia relied for many years on invasive testing and reliable non-invasive tests only recently became available, it would be a great advantage if fetal platelet counts could be measured non-invasively. A development expected soon is reliable assessment of the fetal HPA status using free fetal DNA in maternal plasma instead of amniocentesis. Improved laboratory methods might show a more useful predictive value of antibody levels or antibody function. The use of IVIG seems a relatively 'crude' method to influence immunological processes, and more specific treatment might become available. Again, using the comparison with Rhesus disease, a prophylactic drug similar to anti-D might even be developed.

SUMMARY

FNAIT is one of the major causes of both severe thrombocytopenia and ICH in fetuses and term neonates. The incidence of FNAIT is estimated to be one in 1000–2000

births. Testing for this disorder should be performed on any fetus or neonate with an unexplained ICH and any neonate with unexplained thrombocytopenia, with and without bleeding symptoms.

FNAIT is caused by maternal IgG alloantibodies against HPA on fetal platelets; these alloantibodies cross the placenta. In Caucasians, the immunodominant antigen is the HPA-1a, which is responsible for approximately 85% of FNAIT cases.

The most feared complication of a low platelet count in the fetus or the neonate is ICH and subsequent neurological handicaps.

Over the last 15 years there has been a gradual change in antenatal treatment, from an invasive management protocol to a less invasive management protocol to a completely non-invasive approach. However, there is still controversy over the optimal medical treatment regimen and the role of diagnostic invasive procedures in the management of FNAIT.

Practice points

- The incidence of FNAIT is estimated to be one in 1000–2000 births.
- Testing for FNAIT should be performed for any fetus or neonate with an unexplained ICH and for any neonate with unexplained thrombocytopenia, with and without bleeding symptoms.
- In Caucasians, the immunodominant antigen is the HPA-1a antigen, responsible for approximately 85% of FNAIT cases.
- Pregnancies complicated by FNAIT are best treated with weekly intravenous immunoglobulin. There is no evidence that FBS improves outcome.

Research agenda

- Optimal treatment strategy is not clear.
- Non-invasive management seems to be safe but larger series are needed.
- The mechanisms of action of IVIG in FNAIT need to be elucidated.
- The optimal dose of IVIG is unclear, a multicentre trial (the NOICH study) is ongoing.
- Routine screening of the HPA status of pregnant women needs to be evaluated prospectively for cost-benefit assessment.
- A non-invasive method to predict fetal thrombocytopenia would greatly benefit the management.

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