data were only available from 30 subjects over a period of 27 years. As the incidence of FNAIT is 1:1000 live births, and 600 FNAIT cases can be expected in France per year, we fear that the number of subjects may be too small to draw general conclusions.

More specifically, the following aspects require special attention:

We believe that the design of the study does not allow concluding that no significant correlation exists between the HLA-DRB3 allele and the maternal alloantibody concentration at delivery. Primary data are missing. However, the frequency of this allele among mothers of children with anti–HPA-1a–mediated FNAIT is as high as 98%. Accordingly, a significant difference in the frequency of this allele between any selected groups of mothers is practically excluded a priori and should always prove statistically insignificant.

We also believe that the statistical methods applied to conclude that the most efficacious treatment is maternal therapy with IVIG and steroids are insufficient. The conclusion is drawn from 155 treated pregnancies (not 239 pregnancies as stated in the “Patient cohort” section). Statistical comparisons between platelet counts of newborns assigned to different treatment groups were made with the Mann-Whitney U test, which requires independent samples. This requirement is violated by the fact that the study compares unrelated newborns plus (groups of) siblings born to the same mothers. In addition, the “no treatment” group consists of index cases, that is, (almost exclusively) of first-born babies. This bias may have a systematic influence on platelet counts independent from therapy.

Finally, the authors state that the maternal alloantibody concentration during pregnancy is predictive of fetal thrombocytopenia. Readers should note that the negative predictive value in this study was 75%; accordingly, every fourth unborn will go untreated although it does require treatment. The authors state that their recent study confirms their own data from a previous report. Such a cross-reference is of value if the 2 study groups are independent. We noticed that in the former study, 27 cases were enrolled between 1984 and 2004; and in the recent study, 28 cases were collected from 1981 to 2009. Furthermore, the threshold of the antibody concentration was lowered by a factor of 10 and the scientific and statistical justification for the definition of these different cut-off values is missing.

Taken together, several limitations apply when interpreting this study. Data are not yet sufficient to allow for guiding the management of pregnancies in FNAIT and we should still consider whether antibody concentration will prove helpful in future an open question.

To the editor:

The pathophysiology of FNAIT cannot be deduced from highly selected retrospective data

Today there is no consensus regarding the optimal method for determining the fetal status when the mother has alloantibodies against fetal platelets. Therefore, it was with great interest we read the article by Bertrand et al recently published in Blood. However, we feel that a few points need to be clarified by the authors.

The study1 included 75 women who underwent 239 pregnancies complicated by fetal and neonatal alloimmune thrombocytopenia (FNAIT). Given the same frequency of FNAIT in France as in Norway,2 the yearly expected number of newborns with FNAIT in France would be between 400 and 700. It is surprising that the authors report only the result of 155 pregnancies in Table 2. This represents 0.8%-1.4% of the total number of FNAIT cases occurring in France2 and 4.7%-8.5% of all FNAIT cases in Paris.4 Furthermore, of the 75 women who were studied, we were puzzled to discover the authors present antibody values at delivery from only 30 of these women. The very low number of pregnancies included clearly indicates that the cohort of patients is not a representative selection of FNAIT cases, and in our view it is very unlikely that the authors’ findings can be generalized.

Ensuring homogeneity between groups is very challenging when data collection has taken place over 3 decades. The authors state that “… homogeneity of the subgroups was carefully controlled (cases collected between 1981 and 2009),”1p3209 but they do not explain how they controlled for homogeneity.

Without giving any data, the authors state that “no significant difference emerged between the concentrations of the untreated mothers of blood groups A and O” and they “did not observe any significant correlation between HLA-DRB3 allele and the maternal alloantibody concentration at delivery or the neonatal platelet counts.”1p3210 The reader cannot evaluate whether the lack of significance is because of a type II statistical error, and it is therefore impossible to assess the validity of the authors’ claims.

To predict severe thrombocytopenia from maternal alloantibody levels the authors have calculated sensitivity, specificity, and positive and negative predictive value (see Bertrand Table 4). The

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Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Response

Prediction of the fetal status in noninvasive management of alloimmune thrombocytopenia

Fetal/neonatal alloimmune thrombocytopenia is a severe disease with devastating outcome in severely affected infants. Antenatal interventions suggest the most deleterious consequence, intracranial hemorrhage (ICH), is preventable without known risks for the mother and child. In these circumstances the most challenging issues include development of maternal testing to reliably predict fetal status and allow noninvasive antenatal strategies. Our study is the first to report information both on fetal platelet count and maternal alloantibody concentrations with 3 regimen therapies. Only HPA1b/1b women with a subsequent managed pregnancy served. However the severity of clinical presentation and percentage of primigravida in newly diagnosed cases were very similar to previous larger cohort retrospective reports.

Case reports may overestimate the clinical severity we observed. However the severity of clinical presentation and percentage of primigravida in newly diagnosed cases were very similar to previous larger cohort retrospective reports.

When biologic markers were analyzed careful consideration was given to (1) gestation range. The alloantibody concentration analysis was reviewed only with the first treated pregnancy of each maternal factor may be enrolled after informed consent. Thereafter an index case leading to diagnosis, a complete obstetrical and medical history of the mother is obtained. Obstetricians and gynecologists have been asked to refer all cases of an allo-immune related to thrombocytopenia and other complications of pregnancy. These factors may explain apparent discrepancies between our results and other reports (retrospective versus prospective studies; among the anti–HPA-1a immunized mothers referred to our unit, 20% are not HLA DRB3*0101).

Cases were referred to our unit for therapy counseling; IVIG courses and steroids were therefore given without noticeable variations over the period of time and carefully controlled.

The goal of antenatal management is the prevention of severe fetal thrombocytopenia, with in utero ICH in 80% of cases. A safe fetal platelet count > 50 × 10^9/L may allow vaginal delivery. For ethical reasons no randomized controlled trials have been done for therapy against no treatment. Therefore, only observational studies are available. Reports, in some hundreds of cases, are in favor of maternal therapy with IVIG + steroids. Giers et al report cases with repeated fetal blood samplings (FBS) before each IVIG course potentially playing a role in boosting the maternal immunization possibly explaining the poor results.

In this study without blind allocation the measure of the treatment effect was absence of ICH and the neonatal platelet count. To prevent ICH, the 3 therapeutic regimens were effective. Though each treatment had a failure rate, it is noticeable that combined therapy had the lowest percentage of neonates requiring postnatal therapy. The statistical analysis gave similar results even if siblings are not taken into account (only 51% of the index concentration; therefore certain samples were excluded from analysis in the index cases (4) methodology used for alloantibody concentration (expressed as IU/mL as mentioned in “Methods” not observed by Sachs et al).

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