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.1 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 (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.3 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.

References

authors should have reported the uncertainty of their estimates considering that their calculations were based on only 28 and 37 cases. This could have been done by calculating AUC values and the 95% confidence interval for the ROC curves used for selection of their cutoff values. We are also surprised that the authors did not discuss why their cutoff value was 10 times higher than the cutoff value from a large prospective study.5

The role of IVIg in the treatment of FNAIT is still a matter of debate, and hence it is surprising that the authors do not make reference to the recent studies by Giers et al5-7; these authors could not find any effect of IVIg when given to either the mother or the fetus. The results of the treatment with IVIg and steroids are surprisingly good and may have been because of selection bias.

Jens Kjeldsen-Kragh
Department of Immunology and Transfusion Medicine, Oslo University Hospital; and Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Anne Husebekk
Division of Immunology, University of Tromsø; and Department of Laboratory Medicine, University Hospital of North Norway, Tromsø, Norway

Mette Kjær Killie
Department of Laboratory Medicine, University Hospital of North Norway, Tromsø, Norway

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 after an index case leading to diagnosis, a complete obstetrical and sibling history, data on fetal and neonatal status, and analysis of maternal factors may be enrolled after informed consent. Therefore, among the cases referred to our laboratory, only 75 HPA 1b/1b women fulfilled these requirements (at-risk population) for a total of 239 pregnancies, 66 index cases, and 89 managed pregnancies (contrary to Sachs et al5).

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 reports3-4. 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 mother (2) severity of the disease, platelet count < 50 × 10^9/L (3) timing of maternal samplings: at delivery means samplings done on delivery and NOT during the postnatal period. As reported elsewhere,5 we observed a noticeable increase in the postpartum concentration; therefore certain samples were excluded from analysis in the index cases (4) methodology used for alloantibody concentration6 (expressed as IU/mL as mentioned in “Methods” not observed by Sachs et al5).

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 al5 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

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

Correspondence: Jens Kjeldsen-Kragh, Department of Immunology and Transfusion Medicine, Oslo University Hospital, Kirkeveien 166, 0407 Oslo, Norway; e-mail: jens-kjeldsen-kragh@medisin.uio.no.

References

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Jens Kjeldsen-Kragh, Anne Husebekk, Mette Kjær Killie and Bjørn Skogen