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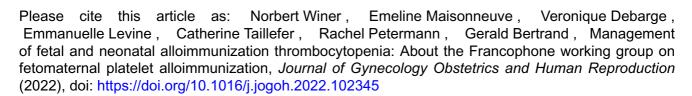
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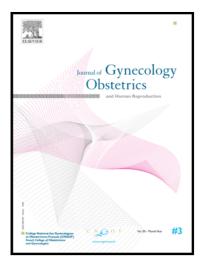
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Letter to the Editor

Management of fetal and neonatal alloimmunization thrombocytopenia: About the Francophone working group on fetomaternal platelet alloimmunization

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What this text adds Messages:

- 1- No absolute scientific consensus exists for management of FNAIT.
- 2- The literature is extremely heterogeneous.
- 3- Evidence has validated the preference in favor of noninvasive management whenever possible.
- 4- Fetal blood sampling can be useful, on a case-by-case basis, after information, traceable in the case file.
- 5- It is unlikely that future large studies will revolutionize knowledge in this field.
- 6- National multidisciplinary group clinical practice guidelines are needed for advice and decision support.

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) occurs in approximately 1/800-1000 live-born neonates. This situation is at high risk of both prenatal and postnatal morbidity and mortality, especially when associated with an intracranial hemorrhage (ICH), caused by the destruction of fetal/neonatal platelets by the transplacental passage of maternal alloantibodies directed against them.

The mode of delivery and the performance of procedures in cases of fetomaternal alloimmunization are not well standardized between centers or even within countries. Over the past decade, management has become increasingly less invasive and moved toward more frequent use of treatments by biologic agents, with the weekly antenatal administration of intravenous

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immunoglobulins (IVIg). Fetal blood sampling (FBS) has been somewhat demonized due to its risks, to the point that many hospitals no longer consider it for any indication. Our objective is to remind clinicians that the arguments given to justify these fears are supported by only a moderate level of evidence and to specify that there is indeed a small window for an obstetric indication, to be determined on a case-by-case basis.

A synthesis by the Royal College of Obstetricians and Gynaecologists (RCOG) and published in the BJOG summarizes the data in the literature (1).

The authors review the level of risk to harmonize professional communication (2, 3) in distinguishing between the following situations:

- Standard risk: mothers with a history of neonatal thrombocytopenia (20- 150×10^9 /L) but without ICH;
- High risk: mothers with a history of severe neonatal thrombocytopenia $(<20 \times 10^9/L)$ but without ICH;
- Very high risk: mothers with a history of severe neonatal thrombocytopenia ($<20 \times 10^9/L$) and early onset of fetal ICH (before 28 weeks).

Moreover, over the past 20 years, management of FNAIT has moved away from invasive prenatal treatment, which sometimes included recurrent FBS and platelet transfusion, and towards noninvasive IVIg administration to the mother as first-line treatment (4). The morbidity and mortality of the cordocentesis or other invasive procedures have been estimated from 6% to 11%, depending on the study, in particular due to the repetition of platelet transfusions and FBS (5,6,7,8). These studies of perinatal risk have, beyond the value of their existence, a particularity: the lack of homogeneity of their indications and of the terms at which they occur, as well as the mixing of simple and therapeutic procedures, although we know that the morbidity of the latter is greater than that of a simple diagnostic needle puncture. The Society for Maternal-Fetal Medicine (SMFM) published a review and guidelines for the use of these procedures and their indications (9). The morbidity of cordocentesis or other needle puncture procedures is thus estimated at 0.5 to 1.5% per procedure (7) — a rate that should reduce the excessive dramatization of its morbidity, especially insofar as it is usually performed by experienced physicians at fetal medicine centers (9). As the dissemination of invasive procedures has halted, it is certain that these invasive fetal procedures cannot be reassessed in a sufficiently large sample.

A multidisciplinary French-speaking working group has been set up to formulate professional guidelines (10) and to be available for decision support for both simple and complex situations, to assist professionals through their regional multidisciplinary prenatal diagnosis centers, including the French pluridisciplinary prenatal diagnosis center (CPDPN).

FBS by cordocentesis remains rare but possible in situations of intermediate risk if there is a question about the indication of medical treatment and, more consensually, in a situation where vaginal delivery is requested. It can be considered after thorough prerequisite information for the patient, since the choice will be made according to the respective benefit-risk balances (for vaginal delivery, operative vaginal delivery, cesarean, and FBS). Multidisciplinary clinical practice guidelines can thus aid physicians with one or more collegial proposals.



References

- 1) Prenatal Management of Pregnancies at Risk of Fetal Neonatal AlloimmuneThrombocytopenia (FNAIT) F Regan, CC Lees, B Jones, KH Nicolaides, RC Wimalasundera, A Mijovic, on behalf of the Royal College of Obstetricians and Gynaecologists, BJOG 2019, paper N° 61 https://doi.org/10.1111/14710528.15642
 https://www.rcog.org.uk/en/guidelinesresearch-services/guidelines/sip61/.
- 2) Pacheco LD, Berkowitz RL, Moise KJ Jr, Bussel JB, McFarland JG, Saade GR. Fetal and neonatal alloimmune thrombocytopenia: a management algorithm based on risk stratification. Obstet Gynecol 2011;118:1157–63.
- 3) Bussel JB, Berkowitz RL, Hung C, Kolb EA, Wissert M, Primiani A, et al. Intracranial hemorrhage in alloimmune thrombocytopenia:stratified management to prevent recurrence in the subsequent affected fetus. Am J Obstet Gynecol 2010;203:135.e1–14.
- 4) Dian Winkelhorst, Michael F. Murphy, Andreas Greinacher et al Antenatal management in fetal and neonatal alloimmune thrombocytopenia: a systematic review: Blood. 2017;129(11):1538-1547
- 5) Birchall JE et al European collaborative study of the antenatal management of feto-maternal alloimmunethrombocytopenia. Br J Haematol **2003**,122:275–88.
- 6) Berkowitz RL, Kolb EA, McFarland JG, Wissert M, Primiani A, Lesser M, et al. Parallel randomized trials of risk-based therapy for fetal alloimmune thrombocytopenia. Obstet Gynecol **2006**;107:91–6.
- 7) Paidas MJ, Berkowitz RL, Lynch L, Lockwood CJ, Lapinski R,McFarland JG, et al. Alloimmune thrombocytopenia: fetal and neonatal losses related to cordocentesis. Am J Obstet Gynecol **1995**;172:475–9.
- 8) Overton TG, Duncan KR, Jolly M, Letsky E, Fisk NM. Serial aggressive platelet transfusion for fetal alloimmune thrombocytopenia: platelet dynamics and perinatal outcome. Am J Obstet Gynecol **2002**;186:826–31. 3

9) Berry SM, Stone J, Norton ME, et al. Fetal blood sampling. Am J Obstet Gynecol 2013;209:170–80G. Bertrand, L. Blouin, F. Boehlen, E. Levine, J.-M. Minon, N. Winer On behalf of the working group on fetomaternal platelet alloimmunization of the French Group of Thrombosis, Hemostasis (GFHT) Archives de Pediatrie 2019,26:191–197192.

