BACKGROUND: Beside titration by indirect antiglobulin test most widely used, anti-D quantitation by continuous flow analysis (CFA) may be performed to assess maternal immunization severity. Only few studies have related its interest in the management of pregnancies complicated by anti-D immunization.

STUDY DESIGN AND METHODS: To demonstrate the relevance of CFA quantitation for the management of pregnancies complicated by anti-D immunization, a retrospective study of 86 severe anti-D immunized pregnancies (anti-D titer \(>\) ou = 16) followed at the Troussseau hospital between 2013 and 2014 was conducted. Concentrations of maternal anti-D were measured by CFA 2-stages method (2SM) (total amount of anti-D) and 1-stage method (1SM) (high affinity IgG1 anti-D). Simultaneously, titrations were performed. These biological data were compared to the severity of the antenatal HDFN (need of IUT, gestational age of the first IUT, fetal cord hemolysis concentration before the first IUT). For 6 severely anti-D alloimmunized pregnant women treated with IVIG and followed at the Troussseau Hospital between 2013 and 2015, the kinetic of anti-D CFA concentrations was analyzed since IVIG introduction and until the first IUT.

RESULTS: The value of IU of anti-D/mL in maternal sera is validated as a threshold to trigger ultrasonographical and doppler fetal surveillance in order to detect fetal anemia. For pregnancies requiring IUT (n=36), maternal 1SM anti-D concentration correlates significantly with the severity and the precocity of the fetal anemia. In the 6 pregnancies with IVIG treatment, anti-D 1SM and 2 SM concentrations significantly decrease after IVIG introduction, suggesting that this treatment may delay the outcome of the fetal anemia in reducing the maternal antibody load.

CONCLUSION: Altogether our results underline the interest of anti-D quantitation by CFA to optimize the management of anti-D alloimmunized pregnancies.

Follow-up of pregnancies complicated by severe anti-D alloimmunisation

Ultrasoundographic surveillance:
Fetal red blood cells hemolysis due to maternal anti-D antibodies could lead to severe fetal anemia, hydrops fetalis and fetal death. In cases of severe maternal alloimmunisation, fetus are monitored every week since 15GW by ultrasonography. Fetal anemia could be diagnosed in a non invasive way by measurement of the peak systolic velocity in the middle cerebral artery (MCA-PSV).

Intrauterine fetal transfusion (IUT):
If severe fetal anemia is diagnosed, fetal red blood cells transfusion could be performed to avoid complications.

Patients in the 'IUT' group have higher anti-D titer, 1SM and 2SM concentrations and 1SM/2SM ratio. The presence of an overlap of anti-D concentrations in the 2 groups shows that anti-D CFA could be only used as screening tests to determine when clinicians should monitor the pregnancy with MCA-PSV measurement. 5 IU/mL appears to be a good threshold. Others factors that have to be determined may condition the fetal outcome (in particular factors which influence the maternal antibody response, the placental transfer of maternal antibodies and the destruction of fetal red cells).

Intrauterine fetal transfusion (IUT) in women at risk of anti-D alloimmunisation ...

Anti-D CFA quantitation appears to be one of the most relevant methods to manage pregnancies complicated by severe anti-D alloimmunization and is the method chosen in the 2 specialized labs in France for the management of dependent cellular cytotoxity tests (RBCs or monocytes) are also a relevant but a more complex alternative and they are performed only in a few countries. Better tests that will take into account both fetal and maternal specific factors need to be developed.

IVIG treatment is performed only in pregnancies at higher risk of early IUT. It induces a diminution of the antibody load in most cases and our results suggest that, in certain cases, it may delay the outcome of the fetal anemia. The mechanism of action of this treatment remains to be established (blockade of FcRn or of activating FcγRI, upregulation of the inhibitors FcγRIB, neutralization of anti-D antibodies by anti-idiotypic antibodies...). Alternative and more efficient immunomodulatory treatment need also to be developed but the difficulty of conducting clinical trials in pregnant women and the absence of relevant murine models makes matters difficult.

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