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IN A NUTSHELL

Pregnancy and childbirth in patients with Glanzmann Thrombasthenia

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Summary
Glanzmann thrombasthenia (GT) is a rare inherited platelet bleeding disorder caused by a quantitative and/or qualitative defect of the αIIbβ3 integrin. Pregnancy and delivery pose special challenges as they entail increased risks of both maternal and foetal bleeding that may be life-threatening. Multidisciplinary management throughout the preconception, intrapartum and peripartum periods is vital to optimize pregnancy outcomes. This Nutshell review focuses on the challenging management of pregnancy and childbirth in patients with GT.

KEYWORDS
bleeding disorders, platelet disorders, pregnancy

Glanzmann thrombasthenia (GT) is a rare, autosomal recessive platelet function disorder caused by quantitative and/or qualitative defects of the platelet glycoprotein (GP) IIb-IIIa (integrin αIIbβ3) receptor.[1] As αIIbβ3 is the major platelet receptor mediating platelet aggregation,[1] GT is characterized by mucocutaneous bleeding with variable expression, ranging from easy bruising to life-threatening haemorrhage.[2] According to the World Federation of Haemophilia survey performed in 2022, there are more than 1700 female patients with GT worldwide.[3] The current literature on pregnancy and delivery in GT patients is based on small case series and scattered case reports,[4,5] which are subject to selection bias, but there are compelling clinical data that pregnancy and delivery in GT patients is associated with an increased risk of bleeding for the mother and the foetus.[4,5] Since there are insufficient data for a comprehensive, evidence-based protocol, this step-by-step review of considerations before, during and after pregnancy, reflects a compilation of published expert opinion and the experience of the authors. A systematic review of management and outcome of pregnancy in GT was published by Siddiq et al. in 2011.[4]

PRECONCEPTION PERIOD

Patients with GT considering pregnancy should be followed at tertiary-care referral centres, with a dedicated multidisciplinary team comprising a haematologist, maternal-foetal medicine specialist, geneticist, anaesthesiologist, neonatologist, laboratory specialist, transfusion medicine specialist, psychologist and pharmacist. Thorough evaluation of the patient should be carried out prior to pregnancy, including ensuring that the patient has completed vaccination against hepatitis B and has undergone assessment of her HLA type in case she will need platelet transfusions. In addition, assessment of the surface expression of αIIbβ3 should be performed since this has implications for the risk of platelet alloimmunization, with higher risk in type 1 GT, defined as <5% surface expression, as well as determination of the molecular biological basis of the disorder, since this has implications for prenatal diagnosis.

Consideration for genomic carrier screening of the partner may be justified in cases of European ancestry based on the estimated prevalence of likely pathogenic GT variants found in ca. 1.3% of the general UK biobank population,[6]

Abbreviations: FNAIT, foetal neonatal alloimmune thrombocytopenia; GP, glycoprotein; GT, Glanzmann thrombasthenia; ICH, intracranial haemorrhage; IVIG, intravenous immunoglobulin; PPH, postpartum haemorrhage.

but population-wide estimates in other groups are not available. Genomic carrier screening of the partner, which can be performed by next generation sequencing, is of higher priority in cases of consanguinity and among specific populations with a high prevalence of GT.[7,8] Tests for HLA-related antibodies, alloantibodies and anti-αIIbβ3 antibodies in the patient's circulation should be performed. Alloantigen assessment can be performed in a reference laboratory or inferred from genomic analysis. A suggested approach for antibody assessment is described in Table S1. Transplacental passage of alloantibodies and antibodies to αIIbβ3, but only very rarely antibodies to HLA determinants, can lead to foetal/neonatal alloimmune thrombocytopenia (FNAIT) with associated severe bleeding, including intracranial haemorrhage (ICH). HLA-related and anti-αIIbβ3 antibodies may limit the value of platelet transfusions since they may produce rapid platelet removal, and anti-αIIbβ3 antibodies may inhibit platelet aggregation if they block fibrinogen binding to platelets. Finally, medical consultation, including haematological assessment for anaemia and iron status, obstetric, ear–nose–throat and dental evaluation should be obtained. The latter two are aimed at addressing conditions that may predispose to spontaneous bleeding or require treatment prior to, or during pregnancy.

Based on these data, risk-stratification is performed. In those with a prior history of life-threatening postpartum haemorrhage (PPH), foetal/neonatal ICH (particularly if fatal or of early onset), high levels of anti-αIIbβ3 antibodies or platelet transfusion refractoriness, pregnancy is considered of particularly high risk and this information should be explicitly conveyed to the patient, ensuring that the patient appreciates the very high risk of pregnancy and delivery for both the patient and the prospective baby. Even patients with GT at lower risk of complications should be counselled regarding the need for close follow-up throughout gestation to optimize pregnancy outcomes.[5] Following shared decision making, after fertility assessment, hormonal therapy is interrupted followed by attempts at conception, realizing that the patient before conceiving may have excessive bleeding with menstrual periods that require therapy.

ANTEPARTUM PERIOD

The use of low-dose aspirin and other antithrombotic agents during pregnancy is contraindicated, including in patients with a history of, or clinical risk factors for, preeclampsia or other placenta-mediated complications. Close monitoring (monthly) of anti-αIIbβ3 immunization status is required. Based on the recommendations and experience accumulated from FNAIT studies,[9,10] in patients with GT who either previously had a thrombocytopenic neonate or have high or rising titres of anti-αIIbβ3 antibodies, antenatal treatment with intravenous immunoglobulin (IVIG) should be considered starting from 20 weeks gestation. In those with prior offspring affected by ICH associated with anti-αIIbβ3 related thrombocytopenia, introduction of IVIG at 12 weeks gestation with adjunctive corticosteroids is recommended. In addition, prenatal monthly sonographic surveillance starting from 16 to 18 weeks gestation is advocated to detect ICH and monitor foetal growth. The presence of anti-endothelial αvβ3 antibodies in the setting of FNAIT has been reported to increase the risk of ICH,[11] but the predictive value of such antibodies in immunized patients with GT remains to be determined.

Generally, there is no increased risk of adverse pregnancy outcomes in patients with GT, including pregnancy loss.[5] Antenatal bleeding events are usually mild and occur at mucocutaneous sites, with relatively low risk of unprovoked, pregnancy-related antenatal bleeding.[4,5] In the event of antenatal bleeding, treatment is determined on a case-by-case basis and depends on the severity of bleeding, history of bleeding and treatment previously used, the gestational age of the foetus, and foetal well-being. Tranexamic acid has been used without evidence of toxicity during the second and third trimesters of pregnancy, as well as during delivery and postpartum period[5]; its use during the first trimester requires caution due to limited available data.

The use of cordocentesis for prenatal diagnosis is now rare because of the relatively high risk of foetal loss.[12] Prenatal diagnosis in GT patients by chorionic villus sampling (CVS) or amniocentesis also carries a risk of bleeding and foetal loss, albeit significantly lower than that associated with cordocentesis. Prenatal diagnosis may be justified, however, in cases of a heterozygous carrier partner, given the 50% risk of having an affected offspring. In this case, it is crucial that the parents understand and are willing to accept the risk. Amniocentesis may confer a lower risk of maternal platelet alloimmunization compared to CVS, based on extrapolations from haemolytic disease of the newborn. Proper haemostatic coverage should be given peri procedurally.[5] There have been exciting advances in maternal blood analyses for detecting foetal genetic alterations, and this would alter the scheme above, but the technology needs to be validated for GT.

DELIVERY AND POSTPARTUM PERIOD

Delivery should take place in a tertiary care setting with an experienced multidisciplinary team because despite prophylaxis, PPH rates of 40–50% have been reported.[4,5] The mode of delivery is usually determined according to obstetrical indications. Caesarean delivery may be preferable in those at high risk of having a thrombocytopenic neonate, based on a prior neonate's history, high levels of anti-αIIbβ3 antibodies, or sonographic findings of ICH. Instrumental vaginal delivery, foetal scalp electrode use and scalp sampling should be avoided in the presence of platelet immunization.[5] If operative vaginal delivery is unavoidable, forceps delivery is preferred over vacuum-assisted delivery. Neuraxial anaesthesia is contraindicated in patients with GT. Intravenous fentanyl

can be used for labour pain management, with general anaesthesia used for caesarean delivery.

Haemostatic coverage is implemented on a case-by-case basis, relying on the use of rFVIIa and/or leuco-reduced platelet concentrates (preferably HLA-matched). If the patient has alloantibodies to HPA-1a, which is on the β3 subunit, because of prior pregnancy or platelet transfusion, the use of HPA-1bb platelets would protect against the platelet clearance effects of the alloantibodies. Prior platelet transfusions may also have elicited anti-HLA antibodies, and these will still pose the risk of platelet refractoriness unless HLA-matched platelets are administered.[13] The adjunctive use of tranexamic acid is supported by expert consensus,[4,5] and should be extended into the postpartum period for at least 3 weeks, and often longer based on the clinical circumstances.[14] Active management of the third stage of labour, including prophylactic administration of uterotonics, early cord clamping and controlled cord traction to assist the delivery of the placenta, is also advocated to limit blood loss. Careful evaluation of vaginal and perineal lacerations and meticulous haemostatic management during caesarean delivery are of utmost importance.[5]

Cord blood should be evaluated for neonatal thrombocytopenia. As the platelet count nadir may occur 3–5 days postnatally, repeat neonatal platelet counts should be obtained, and if low, monitored until normal. In cases of neonatal thrombocytopenia, brain sonographic imaging should be performed within 24 hours after delivery, with platelet transfusion given in the presence of life-threatening bleeding or at platelet counts below which there is concern about the risk of ICH, usually ca. 30×10^9/L.[5] In addition, vitamin K should be administered to the neonate orally instead of intramuscularly.

Based on data from mothers with immune thrombocytopenia purpura, breastfeeding may transmit clinically significant amounts of antiplatelet antibodies.[15] Thus, there is no reason to restrict breastfeeding in GT patients without platelet alloimmunization, but this risk should be considered in those with alloimmunization and when there is persistent neonatal thrombocytopenia.

To prevent further bleeding, including late PPH, which has been reported in up to 25% of patients,[4] early postpartum hormonal therapy to suppress uterine bleeding should be reintroduced. A levonorgestrel-containing intrauterine device has the advantages of not increasing the risk of thromboembolic events or interfering with breastfeeding, while providing adequate suppression of menstrual bleeding and long-term contraception.[16,17]

Immunization status should be reassessed in the postpartum period (at least 6 weeks following delivery) to exclude the occurrence of sensitization in peripartum period (Table S1).

In the future, promising evolving therapeutic agents may be useful in patients with GT. An inhibitor of FcRn, through which maternally derived anti-αIIbβ3 antibodies cross the placenta, may prove effective in the setting of FNAIT, as was initially shown in the analogous haemolytic disease of the newborn.[18] An additional experimental approach being tested in early clinical phase studies in GT patients who are not pregnant involves the use of a bispecific monoclonal antibody that is able to bind both endogenous factor VIIa and the TLT-1 receptor, which is expressed on activated platelets.[19]

Finally, while our recommendations may be applicable in high-income countries, we acknowledge their implementation may be difficult in low- and middle-income countries. Efforts are needed to ensure the GT patients have access to the most medically advanced care globally.

In conclusion, despite the unique challenges pregnancy and delivery entail in the setting of GT, a meticulous multidisciplinary approach can lead to favourable pregnancy outcomes in most cases. The paucity of published data on this topic indicates that there would be considerable benefit in establishing a global registry of pregnancies in patients with GT to better delineate the risks and optimal management.

AUTHOR CONTRIBUTIONS

AR and BSC reviewed the literature and wrote the paper. Both authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declares that he does not have any conflicts of interest.

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N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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