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Case Report

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# Miscarriage in a patient with Glanzmann Thrombasthenia and low ovarian reserve: A case report

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**Abstract**

Glanzmann thrombasthenia (GT), which has an autosomal inheritance pattern, is a hemorrhagic disorder mostly complicated by mucocutaneous bleeding. The severity of this bleeding disorder varies from mild bruising to frequent severe bleeding. Prepartum, peripartum and postpartum bleeding risks are increased in these patients. In addition to the hemorrhagic complications that endanger maternal and fetal well-being, the risk of miscarriage is increased due to maternal antibodies to the platelets found on conceptus-derived trophoblast (placental) cells. In this case report, we report a patient who had a miscarriage in 7+1 week. Our patient had GT, low ovarian reserve, HPV positivity, bilateral dermoid cyst and was complicated by infertility.

**Keywords:** in vitro fertilization, assisted reproductive technics, glanzmann thrombasthenia, miscarriage

## 1. Introduction

Glanzmann thrombasthenia (GT) is a rare autosomal recessive inherited bleeding disorder, first described in 1918, characterized by qualitative and quantitative disorder of αIIbβ3 integrin, a platelet membrane transmembrane glycoprotein (1, 2). Integrin αIIbβ3 has a vital role in platelet functions, thrombus formation and hemostasis in case of injury (3). The encoding gene (*ITGA2B* and *ITGB3)* of αIIbβ3 is located on chromosome 17 with 38 known mutations in glycoprotein IIb and 25 mutations in glycoprotein IIIa (4).

As αIIbβ3 integrin mediates primary hemostasis, the bleeding sites vary in patients with GT: epistaxis (60-80%), gum bleeding (20-60%) and menorrhagia (60-90%) (5). Pregnancy in women with GT has serious risks both for maternal and fetal bleeding. Antepartum, peripartum and postpartum bleeding are pregnancy complications in GT patients. An immune response can be provoked by the passage of B3 integrin expressing fetal cells into the maternal circulation. In response to this passage, maternal antibodies can traversethe placenta and cause neonatal alloimmune thrombocytopenia (NAIT) (6). In a mouse model, antibodies against B3 integrin can promote natural killer cell activation, leading to trophoblast apoptosis in the uterus (7). It is hypothesized that maternal anti-B3 integrin IgG may cause the formation of immune complexes on trophoblast cells, and maternal immune response to fetal antigens can provoke miscarriage (7). In addition, it is reported that maternal anti-B3 integrin IgG antibodies promote intracranial hemorrhage (7).

Here, we report on the case of a 38-year-old patient with GT, complicated by infertility, bilateral dermoid cyst and HPV1 positivity, who had a pregnancy by in-vitro-fertilization resulting in miscarriage in 7+1 week.

## 2. Case report

A 38-year-old Turkish primigravida (in-vitro-fertilization) with GT presented to our infertility clinic for further evaluation and management. She was diagnosed with GT in her childhood with symptoms of frequent nose and gum bleedings. The hematology department regularly reviews the patient. We observed a bilateral dermoid cyst during her infertility evaluation. We conducted a colposcopy, and its result came negative. When she applied at our infertility clinics, her AMH result was 0.76. On her first visit, we observed two follicles in her right ovary. Her partner's sperm parameters were in the range of expected values with a concentration of 103.10^6 and progressive motility of 46%. We provided reproductive genetic counseling to her and her partner. We made a chromosome analysis to exclude any chromosomal associated infertility etiology and detected no chromosomal (46 XX for female and 46 XY for male). Due to the high prolactin levels (table 1), we gave cabergoline treatment before the IVF (in-vitro fertilization) procedure. We did the hematologic workup on her first admission to our infertility clinic (Table 1). These items demonstrated low hemoglobin (10.9 g/dL), hematocrit (34.6 %), MCV (78.6 fl), MCH (24.8 pg), MCHC (31.5 g/dL), PLT (105 K/uL), PCT (0.14 %) and AMH/MIS (0.76 ng/mL) levels (Table 1).

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**Table 1.** Hematologic workup of the patient before the IVF treatment

| Parameter | Results | Unit | Reference Range |
|---|---|---|---|
| WBC | 4.37 | K/ul | 4,.23-10.2 |
| RBC | 4.4 | M/uL | 4.04-5.48 |
| HGB | 10.9 | g/dL | 12.2-16.2 |
| HCT | 34.6 | % | 37.7-47.9 |
| MCV | 78.6 | fl | 80-97 |
| MCH | 24.8 | pg | 27-31.2 |
| MCHC | 31.5 | g/dL | 31.8-35.4 |
| PLT | 105 | K/uL | 142-424 |
| RDW | 17.2 | % | 10-20 |
| MON% | 7.4 | % | 4.7-12.5 |
| MON# | 0.32 | K/uL | 0.24-0.86 |
| BASO% | 0.4 | % | 0.1-1.2 |
| EOS% | 2.5 | % | 0.7-5.8 |
| BASO | 0.02 | K/uL | 0.01-0.08 |
| EOS# | 0.11 | K/uL | 0.04-0.36 |
| NEUT# | 2.02 | K/uL | 1.56-6.13 |
| NEUT% | 46.2 | % | 34-71.1 |
| PCT | 0.14 | % | 0.15-0.7 |
| MPV | 13.4 | fl | 9.1-11.9 |
| PDW | 16.8 | fl | 9-19 |
| LYM% | 43.5 | % | 19.3-51.7 |
| LYM# | 1.9 | K/uL | 1.18-3.57 |
| Prolactin (PRL) | 64.42 | ng/mL | 4.79-23.3 |
| Anti-Mullerian Hormone (AMH/MIS) | 0.76 | ng/mL | 0.14-7. |

Tubal factor infertility was the reason for IVF in this patient. We did a laparoscopic tubal ligation procedure due to bilateral hydrosalpinx before IVF and relaparoscopy was made on the patient with intra-abdominal bleeding after laparoscopy. Postsurgery, two units of blood were transfused, and she was followed up for one night in the intensive care unit. The patient received NovaSeven 2 x 4770 mcg (IV) in the intensive care unit. In the first IVF trial, two oocytes were aspirated with a guide of standard ultrasound equipment and a 19-gauge single lumen needle. After that, we froze two embryos on the third day. There was no vaginal bleeding and intraovarian hemorrhage after the oocyte aspiration procedure. We then transferred embryos in the thaw cycle, but pregnancy did not occur. Afterwards, we made a second attempt. We transferred two embryos on the third day of the fresh cycle, and she conceived in her second IVF attempt. We applied the antagonist cycle was applied in both treatments. We performed ovulation induction with 225 rFSH.

The pregnancy was uneventful until six weeks. We documented anembryonic pregnancy in her 7+1 week control. After one week, she went dilatation and curettage procedure to terminate this anembryonic pregnancy.

## 3. Discussion

GT is one of the most commonly studied autosomal recessive inherited bleeding disorders caused by quantitative or qualitative deficiencies of the αIIbβ3 integrin coded by the ITGA2B and ITGB3 genes located at 17q21–23 (8). Failure of platelet aggregation leads to hemorrhagic complications, which vary from minimal bruising to major bleeding (4).

Pregnancy loss in a patient with Glanzmann thrombocytopenia with low ovarian reserve (AMH: 0.76 ng/mL) who became pregnant with IVF was reported for the first time in our study. Yougbaré et al. reported that maternal anti-B3 integrin IgG antibodies generated during pregnancy traverse the placenta and target paternally inherited antigens on platelets leading to NAIT(7). Furthermore, Yougbaré's study group adds that this B3 integrin antigen is also found in conceptus-derived trophoblast (placental) cells (7). These findings can be the reason for the immune-mediated pregnancy loss of our patient.

Moreover, the ovarian reserve of our patient was low, and her age was advanced (38 years, AMH: 0.76 ng/mL). These factors also can contribute to miscarriage. A meta-analysis focusing on pregnancies with assisted reproductive technology showed that the miscarriage rate is higher in women with low AMH compared to women with a medium or high serum AMH concentration (12,042 women, random-effects model, odds ratio (OR) 1.35; 95% CI, 1.10–1.66; $P = 0.004$; $I2$=50%) (9). Schumacher et al. reported that as AMH levels increase, the risk of pregnancy loss is diminished (10). They also mentioned that women with low AMH levels (AMH ≤ 0.4 ng/mL) are twice as likely to have a miscarriage than women with high AMH levels (AMH ≥ 1 ng/mL) (hazard ratio, 2.3; 95% CI, 1.3, 4.3) (10).

In conclusion, the immune-mediated mechanism due to GT, low ovarian reserve and advanced age of the mother can be the main reasons for miscarriage in this case. An obstetrician, hematologist and anesthetist should follow the pregnancy period of a patient with GT. Patients with GT have multiple risks for both mother and fetal well-being. Preconceptional counseling should be given to the parents to prevent maternal and fetal complications.

### Conflict of interest

The authors declare no conflict of interest.

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### Authors' contributions

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