

Successful twin pregnancy in a common variable immunodeficiency patient: Case study and clinical insights

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ABSTRACT

Common variable immunodeficiency (CVID) is a primary immunodeficiency characterized by an increased vulnerability to recurrent respiratory and gastrointestinal infections, as evidenced by low immunoglobulin levels. Pregnancies in individuals diagnosed with CVID are classified as high-risk due to the considerable variability in disease presentation and potential complications that may arise. Principal concerns during pregnancy associated with CVID include infections, preterm labor, postpartum hemorrhage, thrombocytopenia, and a heightened incidence of eclampsia and pre-eclampsia. We provide a detailed overview of our clinical experience in managing pregnancy for a patient with CVID of a 30-year-old primigravida diagnosed with CVID at 17 weeks of gestation with a twin pregnancy. Implementing targeted care strategies in tertiary healthcare settings is expected to enhance pregnancy outcomes for women diagnosed with CVID.

Key words: Common variable immunodeficiency pregnancy, Intravenous immunoglobulin, Recurrent infections

Common variable immunodeficiency (CVID) is recognized as one of the most prevalent symptomatic primary immunodeficiency disorders, impacting approximately 1 in 25,000 adults globally [1,2]. It most commonly presents between the ages of 20 and 40, with many patients having a prolonged history of recurrent hospitalizations [3,4]. CVID is characterized by an increased susceptibility to recurrent respiratory and gastrointestinal infections due to significantly reduced levels of immunoglobulins (Ig), particularly IgG, IgA, and IgM [5]. The condition is frequently associated with autoimmune diseases, granulomatous disorders, and an elevated risk of malignancies [2].

We present here a case of pregnancy with CVID, its management, and associated clinical insights. The rationale behind presenting this case is that it contributes to the scarce evidence base on pregnancy outcomes in CVID, highlights real-world management challenges, and demonstrates that successful maternal and neonatal outcomes are achievable with coordinated care despite significant risks.

CASE REPORT

A 30-year-old primigravida with CVID presented at 17 weeks of an unplanned pregnancy. She has no

infertility or menstrual issues. Since age 20, she had experienced recurrent upper and lower respiratory and gastrointestinal infections. She was diagnosed with CVID following multiple hospital admissions. In 2015, she experienced severe bronchopneumonia requiring three hospitalizations, with a computed tomography thorax revealing pneumonic consolidation. A detailed immunological evaluation showed severe hypogammaglobulinemia: IgG at 382 mg/dL (reference range: 800–1800), IgA at 26.5 mg/dL (113–563), IgM at 83 mg/dL (54–222), and IgE at 66.5 mg/dL (<150); human immunodeficiency virus test was negative. Genetic testing was not done due to financial constraints.

Following diagnosis, she was initiated on 20 g intravenous Ig (IVIG) therapy (0.5 g/kg/day) every 3 weeks and prophylactic oral antibiotics and vaccines. After receiving five cycles of IVIG, her IgG levels improved to 412.5 mg/dL by 2019, leading to a 3-year period of symptom remission. Four months before her referral at 17 weeks of pregnancy, she was treated with multiple antibiotics, including voriconazole, levofloxacin Category C and D, respectively), acyclovir, and trimethoprim/sulfamethoxazole for recurring symptoms. During this time, she continued monthly IVIG infusions and was managed by the hematology unit, remaining unaware of her pregnancy until 17 weeks. She also received the influenza vaccine in December 2023 and the pneumococcal vaccine in May 2024.

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In May 2024, she presented to the hematology department for further evaluation and was referred to obstetrics after being incidentally diagnosed with a 17-week, 2-day dichorionic diamniotic twin pregnancy. Given the high-risk nature of pregnancy in CVID patients, she was admitted to the obstetrics and gynecology department on September 9, 2024. She was counseled regarding the risks associated with continuing the pregnancy and the potential effects of antibiotics on fetal development. In spite of these, she decided to continue her pregnancy.

During hospitalization, she developed fever, respiratory symptoms, and gastrointestinal disturbances, which were managed with intravenous Piperacillin-tazobactam, metronidazole, and a 20 g IVIG infusion (0.5 g/kg/day). After stabilization, she was discharged with prophylactic cefixime and penicillin. An anomaly scan revealed no congenital abnormalities. At 23 weeks of gestation, she was diagnosed with hypothyroidism and initiated on levothyroxine. Throughout pregnancy, she experienced intermittent fever, cough, and gastrointestinal symptoms, which were managed at a local hospital. At 27 weeks of gestation, she was readmitted with fever, nasal congestion, periorbital pain, and left hypochondriac pain. Hematology consultation was sought, and she was started on IVIG therapy and empirical antibiotics. An ear, nose, and throat Department consultation confirmed sinusitis. She also developed cheilitis, which was managed with methylcobalamin injections. Steroid coverage was initiated in anticipation of preterm labor. During IVIG infusion (a different brand than her previous treatments), she developed a rash and discomfort, requiring cessation and management with an anaphylaxis protocol. The next day, she received the complete IVIG dose with premedication using antihistamines and steroids. Despite ongoing treatment, she continued to have loose stools, managed with Piperacillin-tazobactam, metronidazole, and racecadotril.

Six days into hospitalization, she developed premature contractions and severe abdominal pain. Hematology consultation confirmed no immediate need for IVIG before delivery. In view of the first twin's non-cephalic presentation, an emergency cesarean section was performed. Two preterm female neonates, each weighing approximately 850 g, were delivered through breech extraction. Both infants cried immediately after birth and were admitted to the neonatal intensive care unit (NICU) due to prematurity and low birth weight.

In the postpartum period, the mother continued IVIG therapy and antibiotic treatment. Her respiratory and gastrointestinal symptoms gradually improved. After 52 days in the NICU, both neonates were discharged in stable condition with no postnatal complications. However, the mother faced challenges with IVIG therapy due to its high cost, limited availability, and lifelong necessity.

DISCUSSION

CVID is a primary immunodeficiency disorder characterized by recurrent respiratory and gastrointestinal

infections, requiring multiple hospitalizations. Current research shows that CVID is usually diagnosed in individuals of reproductive age. The index case was also diagnosed during this timeframe. About 30% of CVID patients have a monogenic cause [6]. Research by Maffucci *et al.* suggests that whole-exome sequencing can identify mutated genes associated with CVID, which may follow autosomal dominant patterns, such as those observed in Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1, cytotoxic T-lymphocyte-associated protein 4, and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta mutations, or autosomal recessive patterns, as seen in inducible T-cell costimulator (ICOS), transmembrane activator and CAML interactor, cluster of differentiation 19, B cell-activating factor receptor (BAFFR), cluster of differentiation 20, CD21, and CD27 mutations [7]. However, many cases still lack a definitive cause.

Recurrent bacterial and viral infections may arise from a compromised humoral immune response before diagnosing CVID. It's crucial to rule out other hypogammaglobulinemia causes before confirming CVID. Treatment involves IgG to decrease infections and improve health outcomes, delivered through intravenous infusions (IVIG) or subcutaneous injections (subcutaneous IG [SCIG]), depending on the condition of the patient [8].

Pregnancy in individuals with CVID is considered high-risk due to the disease's variable clinical course and the potential for complications. Key concerns during pregnancy related to CVID encompass infections, preterm labor, postpartum hemorrhage, thrombocytopenia, and the increased incidence of eclampsia and preeclampsia [9].

Gundlapalli *et al.* noted that CVID is not associated with reduced fertility [10]. While CVID does not directly affect fertility, pregnancy in these patients is considered high-risk due to associated complications such as autoimmune cytopenias (autoimmune hemolytic anemia [AIHA], immune thrombocytopenia [ITP], and neutropenia), granulomatous disease, increased malignancy risk, and frequent infections [11]. Our patient did not face infertility challenges and successfully conceived spontaneously.

Standard presentations and investigations were crucial in diagnosing CVID in our patient. Patients with a diminished immune response may exhibit non-infectious symptoms, such as AIHA, ITP, autoimmune neutropenia, and granulomatous manifestations, as well as an increased risk of non-Hodgkin lymphoma and bacterial infections [2,4]. Consequently, pregnancies in these individuals may be riskier than in the general population. Healthcare providers should advise all CVID patients to create a comprehensive pregnancy plan to avoid teratogenic medication intake, especially in the first trimester [9].

Studies indicate that approximately 70% of women with CVID can conceive and successfully carry pregnancies to term with appropriate management [10]. Regular Ig replacement therapy is essential, and caesarean delivery is not routinely required unless obstetric indications

exist [10]. A 2005 study showed high morbidity and mortality in women with CVID, who did not receive IVIG, highlighting the need for IVIG treatment, especially at higher dosages as pregnancy progresses due to physiological hemodilution [12]. Emphasis on adhering to treatment is crucial for these patients.

Early initiation of IVIG therapy, depending on factors like weight gain, gestational age, and Ig levels, is crucial for positive pregnancy outcomes in affected women. Maintaining high Ig levels (above 500 mg/dL) is necessary for adequate infant protection through transplacental transfer after 32 weeks of gestation. However, women in developing countries struggle to access IVIG due to availability and financial issues. In our patient, Ig levels were unstable because of irregular antenatal care, IVIG unavailability, economic difficulties, and challenges resulting from low body mass index (BMI). SCIG and facilitated SCIG (fSCIG) modes were as effective as IVIG, self-administered at home without increased reactions, and well tolerated. However, they were not considered for our patient due to unavailability and cost constraints [8].

Our case study noted adverse reactions to IVIG therapy, highlighting the importance of using a consistent brand and pre-treatment for anaphylaxis. Managing pregnancy in CVID patients requires care at a specialized facility with a multidisciplinary team tailored to individual needs throughout pregnancy. The patient experienced preterm labor due to recurrent infections from unstable IgG, an unplanned pregnancy, and multiple pregnancies. She received IVIG during and after delivery, leading to a positive maternal outcome.

In this case, despite receiving IVIG therapy, the patient's Ig levels remained suboptimal due to irregular antenatal visits, financial constraints, and IVIG unavailability. Studies suggest that early initiation of high-dose IVIG, adjusted for weight gain and gestational age, improves pregnancy outcomes. Administration of 400 mg/kg IVIG every 3 weeks to meet increased immunological demands, ensuring maternal IgG levels remain above 500 mg/dL to facilitate transplacental transfer after 32 weeks of gestation, is recommended [13]. Challenges in this case included an adverse reaction to a different IVIG brand, necessitating premedication with antihistamines and steroids. In addition, the mode of IVIG administration posed difficulties due to the patient's low BMI. SCIG and fSCIG offer alternative options, allowing home-based self-administration with comparable efficacy and reduced systemic reactions. Given the complexities of managing pregnancy in CVID, a multidisciplinary approach is essential. Optimal care involves obstetricians, hematologists, immunologists, and relevant specialists to ensure successful maternal and neonatal outcomes.

CONCLUSION

Pregnancy in patients with CVID requires careful planning, optimized disease control, and access to specialized tertiary care. Key factors for successful outcomes include

adequate preconception counseling, early antenatal care, early initiation of high-dose IVIG with regular monitoring to maintain IgG >500 mg/dL, routine blood investigations to detect cytopenias, protein deficiencies, and infections, prompt treatment of infections with appropriate antibiotics, and close coordination between obstetricians, hematologists, and immunologists.

Despite the challenges posed by CVID, with comprehensive management, pregnancy can be safely carried to term, ensuring both maternal and neonatal well-being.

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