Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
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ORIGINAL ARTICLE

OPEN ACCESS

Pregnancy and lactation in patients with common variable immunodeficiency: a single center experience

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Received 18 July 2025; Accepted 6 October 2025
Available online 1 March 2026

KEYWORDS
newborn;
common variable immune deficiency;
pregnancy;
consanguinity

Abstract
Introduction: Common variable immunodeficiency (CVID) is a primary antibody deficiency characterized by hypogammaglobulinemia and recurrent infections. Studies on the effects of CVID in pregnant patients are still needed. We aimed to investigate the effects of CVID on pregnancy outcomes and newborns.
Methods: We retrospectively evaluated 33 women with CVID and 94 pregnant women at our center. Patients were assessed based on infection rates, pregnancy complications, and use of immunoglobulin replacement therapy (IgRT) in both preterm and post-term periods. Patient data were collected from hospital databases and medical records.
Results: The mean age at first pregnancy was 24.7 (17-45) years, with an average of 2.8 pregnancies per woman. CVID was detected before pregnancy in 24.2% of cases, and 24.2% of patients initiated IgRT during pregnancy. The live birth rate was 69.1%, while early fetal loss occurred in 27.7% of pregnancies, and stillbirth in 3.2%. Infection-related complications occurred in 18% of pregnancies and 14.9% of postpartum periods. The most common infections were upper respiratory and urinary tract infections. Parenteral antibiotic treatment was required for patients who did not receive IgRT during pregnancy. Neonatal infections were observed in 6.6% of cases, and the admission rate to the neonatal intensive care unit was 5.5%.
Conclusion: Our study emphasizes that live birth and fetal loss rates in patients with CVID are comparable to those in the general population. Informing patients of the potential risks associated with consanguinity is crucial. Moreover, given the increased vulnerability of patients with CVID to infections, extra precautions are needed during pregnancy and the postpartum period.

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https://doi.org/10.15586/aei.v54i2.1483

Introduction

Common variable immunodeficiency (CVID) is a heterogeneous disorder characterized by hypogammaglobulinemia and an increased susceptibility to recurrent bacterial infections. It is the most frequently encountered primary antibody deficiency. Numerous studies have demonstrated that immunological and genetic defects play a role in the pathogenesis of CVID.[1-3]

According to the CVID diagnostic criteria, the diagnosis is established based on a significant reduction in IgG levels, along with low IgA and/or IgM levels, in the presence of associated clinical findings, such as susceptibility to infections and multiple autoimmune diseases, including autoimmune cytopenia [e.g., autoimmune hemolytic anemia, immune thrombocytopenic purpura], rheumatoid arthritis, and autoimmune thyroiditis. Additionally, the criteria include isohemagglutinin deficiency or a reduction in switched memory B cells, exclusion of secondary immunodeficiency causes, age of onset older than four years, and absence of a significant T-cell defect.[4,5] However, symptom onset may occur before the age of 4 years, and most individuals diagnosed with CVID are adults between the ages of 20 and 40 years, although cases outside this age range have also been observed.[6]

Pregnancy is characterized by significant adaptations in the maternal immune system.[7] Because the fetus expresses genetically novel antigens, it can be recognized as foreign by the maternal immune system. However, the maternal immune system is typically adapted to tolerate these conditions.[8]

Maternal IgG actively crosses the placenta, with transfer increasing significantly from the second trimester onward and reaching a peak near delivery. Consequently, the newborn acquires passive immunity at birth. The transplacental transfer of maternal IgG does not weaken the overall maternal immune response. Thus, fetal IgG transfer does not result in clinically significant immunodeficiency in the mother or a substantial increase in susceptibility to infections.[9-11] However, maintaining sufficient maternal IgG levels is crucial. In women with immunodeficiency, individualized assessments should be performed based on disease type, severity, and overall health status, and immunoglobulin replacement therapy should be considered when necessary.[12,13]

This study aimed to evaluate the pregnancy and lactation experiences of women diagnosed with CVID and analyze how these physiological processes affect health outcomes. Specifically, the objective was to provide insights into the effects of CVID during pregnancy, the increased risk of infections resulting from immunosuppression, and the challenges faced by women with primary immunodeficiency during pregnancy and lactation. To our knowledge, this is the first study from Turkey to comprehensively analyze pregnancy and neonatal outcomes in women with CVID. Our cohort reflects a geographic population characterized by a relatively high rate of consanguineous marriages, which may influence reproductive outcomes. Furthermore, by reporting detailed neonatal outcomes such as infection rates, birth weight, and intensive care admissions, our study provides novel insights into the early-life impact of maternal CVID. I In doing so, this study aims to inform women with primary immunodeficiency regarding their concerns related to pregnancy and breastfeeding.

Methods

This retrospective, observational, single-center study was conducted in the Department of Immunology and Allergy Diseases at our hospital. It was based on a survey and a retrospective review of patient records.

A total of 33 female patients who had been followed for primary immunodeficiency at the Adult Immunology and Allergy outpatient clinic of our hospital between 2016 and 2024, and who had experienced at least one pregnancy, were included in the study. Data collection forms were completed during routine medical visits, during which patients were asked about their experiences with pregnancy and lactation. Data obtained from the patients were recorded, and informed consent was obtained. Additionally, patient files were reviewed, and relevant information was documented.

Patients were administered immunoglobulin replacement therapy (IgRT) at a dose of 400–600 mg/kg every 3–4 weeks. The IgRT dose was adjusted according to weight monitored during pregnancy.

The diagnosis of CVID was established according to the diagnostic criteria defined by the European Society for Immunodeficiencies (ESID). These criteria require the presence of at least one clinical manifestation, such as increased susceptibility to infections, autoimmune manifestations, granulomatous disease, unexplained polyclonal lymphoproliferation, or a family history of antibody deficiency. In addition, a marked reduction in serum IgG levels together with decreased IgM levels, or a significant reduction in IgA levels even when IgM levels are within the normal range, is necessary. Evidence of impaired antibody responses to vaccination or decreased switched memory B cells relative to age must also be demonstrated. Finally, it is essential to exclude secondary causes of hypogammaglobulinemia, such as infections, protein loss, medication use, or malignancy.[4] Infection data were obtained from patient reports, physician documentation, and laboratory confirmation when available.

Terms used in the article: (i) Miscarriage was defined as intrauterine pregnancy loss before 20 weeks of gestation. (ii) Fetal death was defined as the absence of cardiac activity in a fetus. (iii) Stillbirth (late fetal loss) was defined as the birth of a fetus at ≥20 weeks of gestation with no signs of life. (iv) Preterm birth was defined as birth occurring between 20 and 37 weeks of gestation. (v) Early preterm birth referred to birth occurring between 28 and 31 weeks of gestation. (vi) Late preterm birth referred to birth occurring between 32 and 36 weeks of gestation. (vii) Live birth was defined as a birth in which the infant exhibits signs of life (e.g., crying, breathing, or movement), regardless of gestational age, and the live birth rate was calculated based on all pregnancies (live birth, miscarriage, stillbirth, and others). (viii) The postpartum period was defined as the six weeks following childbirth.[14]

Statistical analysis

Data analysis was performed using IBM SPSS version 23.0. Descriptive statistics for continuous variables were presented as mean ± standard deviation (mean ± SD), median, first quartile, third quartile, and minimum and maximum values. Categorical variables were expressed as frequencies and percentages. The Shapiro-Wilk test was used to assess the normality of the data distribution. Homogeneity of variances for pairwise comparisons was evaluated using Levene's test. Independent two-group comparisons were conducted using the independent samples t-test when the assumptions of normality and variance homogeneity were met, and the Mann-Whitney U test when these assumptions were not satisfied. Comparisons between categorical variables were assessed using the Pearson chi-square test. When necessary, Fisher's exact chi-square test (for 2×2 contingency tables) and the exact chi-square test (for tables other than 2×2) were applied. Statistical significance was set at $P < 0.05$.

Results

Results of 94 pregnancies in 33 women with CVID were evaluated. The mean age of the patients at the time of the study was 50.4 (23-78) years. The mean age at CVID diagnosis was 42.3 (5-72) years. The mean age at first pregnancy was 24.7 (17-45) years. Genetic testing was performed in all patients using Next-Generation Sequencing panels, and no genetic mutations were detected. The mean number of pregnancies per woman was 2.8 ± 0.3 (Table 1).

In the general study sample (n = 33), the rate of consanguinity was 27.3% (n = 9). During their first pregnancy, 9.1% (n = 3) of the participants reported using contraception, and 56.3% conceived within the first year of marriage. The rate of infertility treatment was 12.1% (n = 4), with 3.0% (n = 1) undergoing in vitro fertilization (IVF), 6.1% (n = 2) receiving medication therapy, and 3.0% (n = 1) receiving other medical methods (Table 1). CVID diagnosis was established before pregnancy in 24.2% (n = 8) of the participants, whereas 75.8% (n = 25) were diagnosed post-pregnancy. Before pregnancy, 6.1% (n = 2) received antibacterial prophylaxis due to a history of frequent infections, 3.0% (n = 1) received antiviral prophylaxis, 24.2% (n = 8) received immunoglobulin replacement therapy (IgRT), and 66.7% (n = 22) did not receive any treatment. During pregnancy, 24.2% (n = 8) received IgRT. Among the eight patients diagnosed with CVID before pregnancy, all 11 pregnancies were successfully managed with uninterrupted IgRT therapy (Table 1). Among the 94 pregnancies, 18% (n = 17) were complicated by infection. Infections were reported in 14.9% (n = 14) of the postpartum periods. Infections observed during pregnancy and the postpartum period are presented in Table 1.

A total of 94 pregnancies were analyzed, of which 69.1% (n = 65) resulted in live births. Pregnancy losses included 27.7% (n = 26) early fetal losses and 3.2% (n = 3) late fetal losses (stillbirths). The causes of early fetal loss are listed in Table 2, and the pregnancy outcomes are shown in Table 2. The average birth weight of newborns was 3158.33 g. The gender distribution was equal, with 50% (n = 34) males and 50% (n = 34) females. Neonatal infections were observed in 6.6% (n = 6) of cases, including 4.4% (n = 4) lower respiratory tract infections and 2.2% (n = 2) viral infections. The neonatal intensive care unit admission rate was 5.5% (n = 5), with the most common reasons being preterm birth in four cases (4.4%) and infection in one case (1.1%). One newborn admitted for infection died due to measles two weeks after birth; the mother of this infant was not diagnosed with CVID during pregnancy and therefore did not receive IgRT. Among the participants, 86.2% (n = 56) breastfed their infants, with an average breastfeeding duration of 13 months (3-24). The rate of recurrent fetal loss was 1.5% (n = 1) (Table 2).

When comparing patients diagnosed with CVID before pregnancy and those treated with IgRT during pregnancy with those diagnosed after pregnancy, no statistically significant differences were found in terms of infections. However, all patients who required parenteral treatment for infections during pregnancy were in the IgRT group (Table 3). The 11 pregnancy outcomes of 8 patients who were diagnosed before pregnancy and received IgRT, and the 83 pregnancy outcomes of 25 patients who were diagnosed after pregnancy and did not receive IgRT, are compared in Table 3.

Although the frequency of infection in patients who did not receive IgRT did not differ from that in patients who received IgRT, they were more likely to require parenteral antibiotic therapy due to more severe infections. In this context, patients who did not receive IgRT experienced more severe infections, as indicated by a greater need for parenteral antibiotic treatment. Table 4 shows the rates of early consanguineous marriage, age at first birth, spontaneous abortion, induced abortion based on maternal decision, stillbirth, and infertility in our study population compared with the normal population in Turkey.[15]

Discussion

Pregnancy is an immunologically complex process that requires maintaining an immune balance between the mother and fetus. With recent advancements in diagnosis and treatment, pregnancies in women with CVID are becoming more common, necessitating greater attention to their management.[1] Pregnancy and lactation present various challenges regarding diagnosis, treatment, and long-term complications in women with CVID and hypogammaglobulinemia, and healthcare professionals frequently encounter questions from patients and their families regarding these issues.[16] The management of pregnancy in women with CVID requires a multidisciplinary approach. Immunoglobulin replacement therapy (IgRT) should be planned before pregnancy to ensure optimal immune function and should be regularly maintained throughout gestation.[12,17] Women with CVID, particularly those receiving IgRT, can successfully complete pregnancy. Close medical follow-up, individualized treatment strategies, and multidisciplinary collaboration are essential to ensure optimal outcomes. Given the limited data available on this topic, our study aimed to provide guidance for patients diagnosed with CVID during pregnancy and lactation. A key strength of our study is its focus on a Middle Eastern cohort with

Table 1 Pre-pregnancy and pregnancy-related data in patients with CVID.

Variables	n (%)
Patient Demographics and General Data	
Total CVID patients, n	33
Mean follow-up period of CVID patients (years)	8.09
Age at first pregnancy mean (minimum- maximum)	24.7(17-45)
Age at last pregnancy mean (minimum- maximum)	28.4(23-45)
CVID diagnosis age, mean (minimum- maximum)	42.3 (5-72)
Mean number of pregnancies (mean ± SD)	2.8 ± 0.3
Pre-Pregnancy Evaluation	
Patients with consanguineous marriage, n (%)	9 (27.3)
Pregnancies in consanguineous marriage (%)	24(25.5)
Patients who used contraception before their first pregnancy, n (%)	3 (9.1)
Time to first pregnancy after marriage (mean ± SD, months)	17.8 ± 3.2
Patients Receiving Infertility Treatment	
In vitro fertilization	4 (12.1)
Medication	1 (3.0)
Other treatments	2 (6.1)
When to Diagnose CVID	
Pre-pregnancy	8 (24.2)
During pregnancy	0
Post pregnancy	25 (75.8)
General data according to the number of pregnancies, (n: 94)	
Pre-pregnancy Prophylaxis Treatment, n (%)	
Antibacterial treatment	2 (2.1)
Antiviral therapy	1 (1.05)
IgRT therapy	11 (11.7)
SCIG	0
IVIG	11
Types of Infections During Pregnancy, n (%)	
Upper respiratory tract infection	8 (8.5)
Pneumonia	2 (2.1)
Lower respiratory tract infection with asthma attack	2 (2.1)
Urinary tract infection	5 (5.3)
Hospitalization due to infection during pregnancy, n (%)	3 (3.2)
İnfections in the postpartum period (first 6 weeks), n (%)	
Upper	10 (10.7)
Pneumonia	2 (2.1)
Caesarean section wound infection	2 (2.1)
Mastitis (infection or abscess requiring antibiotics)	10 (10.6)
Hospitalization due to infection in the postpartum period, n (%)	1 (1.1)

CVID: Common variable Immune deficiency, IgRT: Immunoglobulin replacement therapy, SCIG: Subcutaneous immunoglobulin, IVIG: Intravenous immunoglobulin.

distinctive demographic characteristics, including a high prevalence of consanguinity, offering new perspectives on how genetic and environmental factors may interact with immunodeficiency to influence pregnancy and neonatal outcomes. Additionally, the detailed analysis of neonatal complications, including infection and NICU admission rates, provides valuable data that are rarely reported in previous studies.

In the PREPI study, which examined the pregnancy outcomes of 93 women diagnosed with primary immunodeficiency, 154 (69%) of 222 pregnancies resulted in live births.[18] Similarly, a 2015 study by Gundlapalli et al. investigated the pregnancy outcomes of 385 women with CVID and hypogammaglobulinemia and reported an overall live birth rate of 72%.[19] The live birth rate of 69.1% in our study was broadly consistent with these findings. However, in a study by Kraličková et al., which analyzed 115 pregnancies in 54 women with CVID, the reported live birth rate was 77%.[20] This discrepancy may be attributed to differences in population characteristics, immunodeficiency types, or pregnancy management approaches. It should be noted that both spontaneous abortions and induced abortions are included in the total number of pregnancies when calculating this rate. In contrast, ACOG excludes abortions

Table 2 Pregnancy outcome, breastfeeding period, and neonatal period evaluation.

Variables	n (%)
Total number of pregnancies	94
Live birth	65(69.1)
Early fetal loss	26(27.7)
Late fetal loss (number of stillbirths)	3(3,2)
Causes of early fetal loss	
Spontaneous abortion	17(18.1)
Fetal Anomaly	1(1,1)
Fetal death	3(3,2)
İnduced abortion that were the mother's decision	4(4.3)
Uterine anomaly	1(1,1)
Late fetal loss (cause of stillbirth)	
Unknown:	2(2.1)
Hydrocephalus:	1(1,1)
Pregnancy result	
On time birth	49(52.1)
Fetal loss	29(30.9)
Ectopic pregnancy	0
Premature birth (<37)	10(10.6)
Very premature birth (<32)	4(4.3)
Late birth	2(2,1)
Method of birth	
Vaginal	54(79.4)
Caesarean	14(20.6)
Bleeding requiring blood transfusion during delivery	1(1,1)
Recurrent fetal loss	1(1.5)
Baby died in the neonatal period	1(1.5)
Baby birth weight (average) Min-max	3158.3(1400-4100)
Female, n (%)	34(50)
Infection in the baby during the neonatal period	
Pneumonia	4(4.4)
Viral infections (measles, adenovirus)	2(2.2)
History of neonatal intensive care or hospitalization	
Due to premature birth	4(4,4)
Infection related	1(1,1)
Number of mothers breastfeeding their babies	56(86.2)
Average breastfeeding duration, months (Min-max)	13 (3-24)

Table 3 Comparison of patients who received and did not receive IGRT treatment during pregnancy.

	IGRT recipient n (%)	Non- IGRT n (%)	P value
Total pregnancy (n:94)	11(11.7%)	83(88.3%)	
Infection during pregnancy	2(18.2%)	15(18.1%)	0.633
Severe infection requiring parenteral treatment	0	3(3.6%)	0.524
Postpartum infection	2(18.2%)	12(14.5%)	0.746
Infection during breastfeeding	2(18.2%)	12(14.5%)	0.746
Mastitis history	2(18.2%)	8(9.6%)	0.331
Miscarriage or stillbirth	3(27.3%)	26(31.3%)	0.786

IgRT: Immunoglobulin replacement therapy

and considers only live births and stillbirths when calculating the live birth rate.

Regarding early fetal loss, our study identified a rate of 27.7%, which is notably higher compared with 22% in the PREPI study, 19% in the study by Gundlapalli et al., and 10.4% in the study by Kraličková et al. This higher rate may be linked to the relatively high prevalence of consanguinity in the Turkish population, which is associated with increased genetic risks. Additionally, four women in the early fetal loss group underwent voluntary termination of

Table 4 Birth-related rates in our study population compared with the normal population in the TNSA.

Variables	TNSA 2018	CVID patients
Consanguineous Marriage (%)	24.0	25.5
Age at First Birth (years)	23.3	24.7
Spontaneous Abortion (%)	13.0	18.1
Induced abortion (mother's decision), (%)	6.0	4.3
Stillbirth (%)	1.0	3.2
İnfertility (%)	12	12.1

CVID: Common variable Immune deficiency, TNSA: Turkey Demographic and health Survey

pregnancy, which may have contributed to the increased miscarriage rate. Our study demonstrated a significantly higher spontaneous abortion rate among women with consanguinity. Furthermore, the association between primary immunodeficiencies and consanguinity has been highlighted in the literature.[21,22] Our findings regarding late fetal losses (stillbirths) were comparable to those of previous studies. The timely birth rate among patients (52.1%) was higher than that reported in the PREPI study, whereas the preterm birth rate was lower. This difference may be related to the inclusion of primary immunodeficiency diseases other than CVID in the PREPI cohort. The data in our study are similar to those of the general population with respect to term and preterm birth rates and indicate that the risk of preterm birth is not increased in patients with CVID. The preterm birth rate (10.6%) in our cohort is consistent with WHO data. In this study, pregnancy-related loss and birth rates in 94 pregnancies were compared with reference values from the World Health Organization (WHO) and the American College of Obstetricians and Gynecologists (ACOG). The early fetal loss rate in our study was 27.7%, considerably higher than the 10% reported by ACOG. This discrepancy may be attributed to the inclusion of higher-risk pregnancies in our population or differences in diagnostic and follow-up practices. The rate of late fetal loss (stillbirths) was 3.2%, which is higher than the 1.39% global average reported by WHO but lower than the 4.4% reported by ACOG. The preterm birth rate (<37 weeks) was 10.6%, comparable to both the WHO estimate of 10% and the ACOG range of 10–12%. The very early preterm birth rate (<32 weeks) was 4.3%, slightly above the 2.8% noted by ACOG. Taken together, these findings suggest that pregnancies in our cohort are associated with a higher risk of early fetal loss compared with the general population, while preterm birth rates remain consistent with international data.[23-25]

In our study, four patients (12.1%) received infertility treatment. According to the World Health Organization (WHO), the infertility rate in women is 17%, while infertility affects up to 12% of reproductive-aged couples according to TNSA, and up to 15% according to the American College of Obstetricians and Gynecologists.[15,26,27] One patient was diagnosed with CVID during evaluation for infertility, diarrhea, weight loss, and recurrent infections and achieved spontaneous conception two months after initiating IgRT. This patient had two pregnancies while receiving IgRT and delivered healthy term infants without infection during pregnancy or lactation. IgRT was started at a dose of 400 mg/kg, adjusted according to body weight, for the diagnosis of CVID. These findings highlight the potential anti-inflammatory and immunomodulatory effects of immunoglobulin therapy.[28,29] However, it cannot be concluded from a single case that initiating IgRT prevents early fetal loss or infertility. Uncontrolled immune responses in early embryonic development may contribute to infertility and reproductive failure, and immunosuppressive or immunomodulatory therapies such as IgRT may help prevent immune-mediated embryonic attacks, as supported by several studies.[30,31] Among the other infertility-treated patients in our study, one conceived via in vitro fertilization (IVF), two through medication therapy, and one through other medical methods.

In our study, patients who received IgRT during pregnancy did not experience an increased frequency of infections, did not require hospitalization for severe infections, and had smoother pregnancies overall. In contrast, three women who were diagnosed with CVID postpartum developed severe infections requiring hospitalization, further supporting the efficacy of IgRT in reducing infection-related complications during pregnancy.[18] A case series has also indicated that IgRT dosages were appropriately adjusted during pregnancy.[12,32]

In the PREPI study conducted on immune deficiency, it was reported that 58% of the 122 women examined continued breastfeeding during the postpartum period, and 12 patients developed mastitis or abscess.[20] In our study, 55 patients (86.2%) who delivered live births stated that they breastfed their babies during the postpartum period, and 10 patients (10.3%) developed mastitis. These results indicate that the breastfeeding tendencies of women with CVID during pregnancy and postpartum are similar to those of healthy pregnant women in the general population.[33]

The average birth weight in our study was consistent with that of the general population. However, the PREPI study emphasized that the risk of low birth weight is higher in infants born to mothers with primary immune deficiencies; therefore, the finding of a normal birth weight range in our cohort is considered a positive outcome.

Conclusion

Pregnant women receiving IgRT had a lower risk of severe infections than those who did not receive IgRT. Additionally, our study found that in patients with CVID, live birth rates, infertility rates, mode of delivery, term birth rates, preterm birth rates, and neonatal weights were comparable to those in the general population. This finding suggests that a well-planned treatment program for pregnant women with CVID can be beneficial in managing infections and in reducing anxiety throughout pregnancy and the postpartum period.

It is important to emphasize that live birth and fetal loss rates in patients with CVID do not differ significantly from those in the general population. However, patients should be informed of the potential risks associated with

consanguinity. Moreover, patients with CVID are particularly susceptible to infections, necessitating additional precautions. Notably, pregnant women receiving IgRT appeared to have a smoother pregnancy course with a lower incidence of complications including infections and hospitalizations.

Limitations

Our study had a limited sample size, and further research with a larger cohort is warranted. Although the retrospective design and small number of participants, resulting from the rarity of CVID, are important limitations, the study still provides meaningful data that contribute to the scarce literature on this condition. The relationship between breastfeeding and neonatal infections could not be thoroughly evaluated due to the limited number of cases. Therefore, large-scale prospective studies are essential to address existing knowledge gaps and to establish optimal management strategies in this field.

Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that no AI-assisted tools were used in the preparation of this manuscript. All references have been manually verified for accuracy and relevance.

Author Contributions

All authors contributed equally to this article.

Conflicts of Interest

The authors declare no conflict of interest.

Funding

None.

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