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Spontaneous Conception After Treatment-Associated Premature Ovarian Insufficiency Following Chemoradiotherapy and Allogeneic Stem Cell Transplantation for Acute Lymphoblastic Leukemia

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Abstract

This rare case describes a 34-year-old woman who spontaneously conceived after intensive chemoradiotherapy followed by bone marrow transplantation. She was diagnosed with KMT2A-rearranged acute lymphoblastic leukemia in June 2019, when she was approximately 10 weeks pregnant at her booking appointment. The pregnancy was terminated to enable urgent initiation of treatment. She subsequently received intensive chemotherapy, radiotherapy, including total body irradiation (TBI), and allogeneic hematopoietic stem cell transplantation in 2019. Following treatment, she experienced prolonged amenorrhea and menopausal symptoms, and premature ovarian insufficiency was diagnosed. She was counseled that natural conception was unlikely. Donor-oocyte treatment was considered an option for secondary subfertility. In 2026, she conceived spontaneously. The pregnancy was not recognized until approximately 23 weeks' gestation. It was unexpected because of her longstanding premature menopause. This pregnancy was also complicated by anti-C antibodies due to multiple blood transfusions. During her pregnancy, she was managed by a multidisciplinary team and underwent close antenatal monitoring. Serial monitoring of antibody levels and ultrasound examinations demonstrated normal fetal growth and Doppler findings. At 35 weeks' gestation, she experienced spontaneous rupture of membranes and preterm labor, resulting in the delivery of a live male infant.

Categories: Obstetrics/Gynecology, Transplantation, Oncology
Keywords: acute lymphoblastic leukemia (all), allogenic stem cell transplant, fertility issues, pregnancy after transplant, premature ovarian failure, spontaneous pregnancy, total body irritation

Introduction

Improved survival following hematological malignancy has resulted in increasing numbers of women living with the reproductive consequences of cancer treatment. Gonadotoxic chemotherapy, radiotherapy, and conditioning regimens used before hematopoietic stem cell transplantation (HSCT) can deplete the ovarian follicular reserve and cause menstrual dysfunction, premature ovarian insufficiency (POI), and infertility. The degree of reproductive toxicity depends on age at treatment, pretreatment ovarian reserve, cumulative chemotherapy exposure, and the conditioning regimen used [1,2].

Alkylating agents are particularly associated with ovarian toxicity, while total body irradiation (TBI), used as part of myeloablative conditioning, can cause substantial ovarian damage. Studies of female HSCT survivors have demonstrated impaired ovarian function following allogeneic transplantation, particularly after TBI-containing conditioning regimens [1,2]. Nevertheless, ovarian function and reproductive recovery vary between individuals, and menstrual activity and spontaneous conception may occur in a minority of women despite previous gonadotoxic treatment [2,3].

Pregnancy following HSCT remains uncommon but is well documented. An early European survey reported successful pregnancies following bone marrow or peripheral blood transplantation and identified increased risks of preterm delivery and low birth weight [4]. Subsequent cohort and registry studies have confirmed that spontaneous pregnancies can occur after HSCT, including among women exposed to TBI and high-dose chemotherapy [3,5,6].

A systematic review and meta-analysis published in 2019 estimated pooled pregnancy rates of approximately 25% following autologous HSCT and 22% following allogeneic HSCT (allo-HSCT), although substantial heterogeneity existed between studies [7]. In a national multicenter study published in 2024, 74 pregnancies were identified among 50 women following allogeneic hematopoietic cell transplantation (allo-HCT). Of these pregnancies, 72% occurred spontaneously. TBI exposure was associated with a lower likelihood of pregnancy [8]. More recently, a 2026 international multicenter European Society for Blood and Marrow Transplantation (EBMT) study reported 621 pregnancies among 419 patients or partners in a cohort

of 54,323 HCT recipients. Of these pregnancies, 318 occurred in female recipients. The study demonstrated variation in pregnancy occurrence according to conditioning regimen and highlighted the contribution of assisted reproductive technology (ART), including donor oocytes, to pregnancy after transplantation [9].

Current international guidance on POI emphasizes appropriate diagnosis and individualized fertility counseling, recognizing that ovarian insufficiency does not invariably indicate a complete and permanent absence of ovarian activity [10]. Similarly, cancer fertility-preservation guidelines recommend discussing reproductive risks at cancer diagnosis and providing timely access to fertility-preservation specialists when gonadotoxic treatment is planned [11].

Despite growing evidence that pregnancy can occur after HSCT, reliable predictors of ovarian recovery remain limited, particularly after TBI. Women with prolonged amenorrhea and menopausal symptoms are therefore commonly counseled that conception without donor oocytes is unlikely, and the possibility of spontaneous pregnancy may be underemphasized in contraception and fertility counseling. This case report aims to illustrate that spontaneous conception and successful pregnancy can occur even after TBI, allo-HSCT, and a prolonged period of apparent ovarian failure, and to highlight the implications for individualized counseling and follow-up of reproductive function in this population.

Case Presentation

A 34-year-old woman was diagnosed with KMT2A-rearranged acute lymphoblastic leukemia (ALL) in June 2019. At diagnosis, she was approximately nine to 11 weeks pregnant. The pregnancy was terminated to permit urgent treatment of her hematologic malignancy. She subsequently underwent intensive chemotherapy and radiotherapy, including TBI, followed by allo-HSCT in 2019. Before her leukemia diagnosis, she had one healthy child in 2018 without reported complications. Following cancer treatment and transplantation, she developed prolonged amenorrhea and premature menopausal symptoms. She was diagnosed with POI (Table *1*). Follicle-stimulating hormone (FSH) levels were 85.9, 73.7, and 58.7 IU/L (February 2024, November 2024, and March 2025). All were well above the 25 IU/L threshold, and the first two were more than four weeks apart, as per POI diagnostic criteria. Estradiol was below the detection limit (<62, then <58 pmol/L). Anti-Müllerian hormone was <0.2 ng/mL in December 2020.

Time point	FSH (IU/L)	Luteinizing hormone (IU/L)	Estradiol (pmol/L)	Anti-Müllerian hormone (ng/mL)
December 2020	NA	NA	NA	<0.2
February 2024	85.9	56.1	<62	Not performed
November 2024	73.7	NA	NA	NA
March 2025	58.7	24.7	<58	NA

TABLE 1: Hormone levels for diagnosis of POI.

FSH, follicle-stimulating hormone; POI, premature ovarian insufficiency

By these values, and with amenorrhea, the patient met the biochemical criteria for POI by November 2024 at the latest. She was about 38 years old at the first FSH measurement. FSH fell steadily from 85.9 to 58.7 IU/L over 13 months, and luteinizing hormone fell from 56.1 to 24.7 IU/L. She was counseled that her fertility was likely to be severely impaired and that donor-oocyte treatment might be required if she wished to pursue pregnancy in the future. Hormone replacement therapy was commenced to manage hypoestrogenic symptoms. Several years after transplantation, spontaneous conception occurred in 2026. The pregnancy was unplanned and remained unrecognized until approximately 23 weeks' gestation. Retrospectively, the patient reported abdominal bloating for several weeks and perceived fluttering movements, initially attributed to gastrointestinal symptoms. Following confirmation of pregnancy, she was referred for specialist antenatal care. The pregnancy was considered high risk because of her previous hematologic malignancy, intensive treatment, TBI, and allo-HSCT.

Anti-C red-cell antibodies were also identified during pregnancy, attributable to multiple blood transfusions in the past. The anti-C level was reported as <7.5 IU/mL at the start and subsequently <7.5 IU/mL during pregnancy (normal values; Table *2*). Appropriate serial fetal surveillance was undertaken with ultrasound monitoring, and all findings were normal.

Time point	Anti-C level (IU/mL)
July 2026	5
July 2026	5.3
August 2026	5.2

TABLE 2: Anti-C levels.

Ultrasound assessment demonstrated reassuring fetal growth, amniotic fluid volume, and Doppler studies. Estimated fetal weight was approximately at the 33rd centile. Middle cerebral artery peak systolic velocity remained below 1.5 multiples of the median, with no ultrasound evidence suggestive of significant fetal anemia due to anti-C antibodies.

At 35 weeks' gestation, the patient presented with spontaneous rupture of membranes and subsequently developed preterm labor. She delivered a live male infant with Apgar scores of 7 at one minute, 8 at five minutes, and 9 at five minutes and a weight of 2868 g. Both maternal and neonatal postnatal courses were satisfactory, and the patient was discharged from the hospital (Figure *1*).

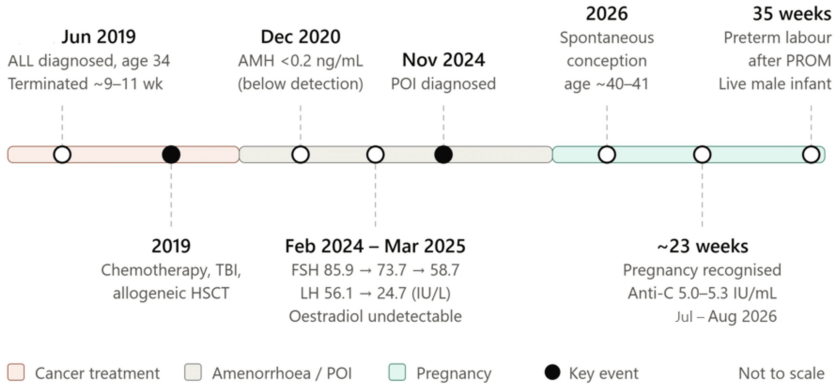


FIGURE 1: Timeline of clinical course.

ALL, acute lymphoblastic leukemia; AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; HSCT, hematopoietic stem cell transplantation; LH, luteinizing hormone; POI, premature ovarian insufficiency; PROM, premature rupture of membranes; TBI, total body irradiation

Discussion

The principal feature of this case is spontaneous conception following treatment for ALL with intensive chemotherapy, TBI, and allo-HSCT, despite prolonged amenorrhea, menopausal symptoms, and previous counseling that spontaneous fertility was unlikely.

The ovary is highly sensitive to cytotoxic chemotherapy and ionizing radiation. Alkylating agents can deplete primordial follicles, while TBI can cause substantial follicular loss and ovarian endocrine dysfunction. Treatment intensity, age at exposure, and the conditioning regimen influence the extent of ovarian damage [1,2]. Ovarian function following allo-HSCT varies considerably, and TBI-containing conditioning regimens are associated with an increased risk of ovarian failure [2,3].

Despite the high risk of infertility, spontaneous pregnancy after HSCT has repeatedly been reported [3-6]. In a retrospective study of female survivors of childhood allo-HSCT, six of 37 women reported spontaneous pregnancies resulting in eight live births. Pregnancies occurred among women exposed to TBI and high-dose chemotherapy, as well as among women treated with chemotherapy alone [5]. These findings demonstrate that spontaneous conception remains possible in some women despite intensive treatment and previous evidence of impaired ovarian function.

The 2019 systematic review and meta-analysis provides further context, estimating pooled pregnancy rates of approximately 25% following autologous HSCT and 22% following allo-HSCT [7]. These estimates should

be interpreted cautiously because the underlying studies differed in patient characteristics, follow-up duration, conditioning regimens, fertility-preservation practices, and definitions of pregnancy. They should not be interpreted as an individual patient's probability of spontaneous conception.

The 2024 national multicenter study provides contemporary evidence particularly relevant to this case. Among 74 pregnancies identified in 50 women following allo-HCT, 72% occurred spontaneously. Pregnancy was less frequent among women exposed to TBI, but spontaneous conception remained possible [8]. The 2026 international EBMT study provides a larger contemporary dataset. Among 54,323 HCT recipients, pregnancy rates of 22-25% were reported. ART was used by 33% of female patients with available conception data, and donor eggs were more frequently used than stored autologous reproductive material among female recipients [9]. These findings demonstrate that pregnancy after transplantation may occur through spontaneous conception or assisted reproductive interventions, depending on individual circumstances and previous treatment.

The 2025 international POI guideline recommends diagnosing POI in women younger than 40 years based on disordered menstrual cycles and biochemical evidence of ovarian insufficiency [10]. Nevertheless, predicting reproductive recovery after HSCT remains difficult. Menstrual activity, ovarian endocrine function, and the ability to conceive are related but distinct outcomes. Therefore, prolonged amenorrhea and previous counseling about severe fertility impairment should not be interpreted as definitive evidence that spontaneous conception cannot occur.

The case has important implications for counseling. Contemporary fertility-preservation guidelines recommend discussing reproductive risks before gonadotoxic cancer treatment and offering appropriate fertility-preservation options where feasible [11]. However, acute leukemia presents particular challenges because treatment often needs to commence urgently, potentially leaving little opportunity for conventional fertility preservation.

For women who develop ovarian insufficiency following treatment, counseling typically emphasizes impaired fertility and the potential need for assisted reproductive interventions, including donor oocytes. Nevertheless, ovarian function can recover spontaneously and unpredictably [5,8,9]. Consequently, women with prolonged treatment-associated amenorrhea should not assume that pregnancy is impossible. Contraceptive options should be discussed when pregnancy is not desired. This consideration is particularly important in the present case, as the patient did not recognize her pregnancy until approximately 23 weeks' gestation.

Pregnancy after HSCT may carry increased obstetric risks. The European survey by Salooja et al. reported adverse pregnancy outcomes, including preterm delivery and low birth weight, among pregnancies following transplantation [4]. A subsequent CIBMTR report described 178 pregnancies, including 83 pregnancies in female transplant recipients and 95 in female partners of male recipients. Live births were reported in 85% of pregnancies among female recipients [6]. More recent literature suggests that uterine and placental effects of previous irradiation may contribute to adverse pregnancy outcomes in addition to ovarian toxicity. Gazzo et al. described two pregnancies following HSCT with TBI-containing conditioning and reported significant fetal growth restriction, with findings suggesting impaired placental development [12]. However, these observations arise from a small case series and do not establish causation.

The patient developed spontaneous rupture of membranes and preterm labor at 35 weeks' gestation. Although this constituted a preterm birth, the pregnancy resulted in a live birth with satisfactory maternal and neonatal outcomes. The pregnancy also required surveillance for anti-C red cell antibodies. Serial assessments demonstrated reassuring fetal growth and Doppler findings, with middle cerebral artery peak systolic velocity remaining below 1.5 multiples of the median and no evidence of significant fetal anemia.

This case illustrates the unusual combination of prolonged treatment-associated amenorrhea, previous TBI and allo-HSCT, counseling regarding probable severe fertility impairment, and subsequent spontaneous conception resulting in a live birth. It emphasizes the importance of individualized fertility and contraception counseling, as well as multidisciplinary obstetric follow-up and appropriate antenatal surveillance for women who conceive after allo-HSCT, taking into account previous conditioning regimens, potential uterine and placental effects, and individual obstetric risk factors.

Conclusions

Spontaneous conception can occur following intensive chemotherapy, TBI, and allo-HSCT despite prolonged amenorrhea and markedly reduced expected fertility. This patient was planning to pursue pregnancy through in vitro fertilization with donor oocytes but conceived spontaneously. The pregnancy was diagnosed late because it was unexpected and the symptoms were vague. This case reinforces that treatment-associated amenorrhea and POI should not be regarded as definitive proof of sterility. Women surviving hematological malignancy should receive individualized counseling regarding both fertility and contraception.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Shagufta Nawaz

Acquisition, analysis, or interpretation of data: Shagufta Nawaz

Drafting of the manuscript: Shagufta Nawaz

Critical review of the manuscript for important intellectual content: Shagufta Nawaz

Disclosures

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