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Successful Live Birth in a 42-Year-Old Chinese Female Survivor with Acute Lymphoblastic Leukemia Following Obtained Autologous Viable Embryo at 41-Year-Old via Intracytoplasmic Sperm Injection: A Case Report and Literature Review

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Abstract

Objective: To report a healthy live birth in a 42-year-old advanced age woman who obtained autologous oocyte at 41-year-old via Intracytoplasmic Sperm Injection (ICSI) and formed her own only viable embryo. She developed into Premature Ovarian Insufficiency (POI) after allogeneic Hematopoietic Stem Cell Transplantation (HSCT) following her diagnosis of Acute Lymphoblastic Leukemia (ALL) 23 years ago.

Design: Case report

Setting: Reproductive Medicine Center of Obstetrics and Gynecology, Nan fang Hospital, Southern Medical University.

Patient: A 42-year-old nulliparous Chinese woman underwent allogeneic HSCT at the age of 19 for diagnosis with ALL. She had infertility for 14 years. The initial measurement of Anti-Müllerian Hormone (AMH) was 0.158 ng/ml and the Antral Follicle Count (AFC) was 3 in the left ovary and 1 in the right ovary according to transvaginal ultrasound detection.

Interventions: In Vitro Fertilization-Embryo Transfer (IVF-ET) had been performed for her. After 3 Cycles of Ovarian mild Stimulation (COS) and oocyte retrieval attempt, only 2 eggs were obtained via ICSI at her 41-year-old and 1 available embryo was formed. She accepted Frozen-thawed Embryo Transfer (FET) at her 42 -year-old.

Main outcome measures: A healthy live birth after ICSI and FET with her own oocyte.

Results: A 42-year-old advanced age woman who underwent allogeneic HSCT at the age of 19 for diagnosis with ALL successfully conceived with her own only oocyte obtained at her 41-year-old by means of ICSI and FET. Only one viable embryo was transferred under the treatment of hormone replacement therapy and frozen-thawed embryo transfer at 42-year-old, resulting in a pregnancy and full-term normal delivery induced by oxytocin at 39 weeks and 3 days of a healthy male baby weighing 3,140g.

Conclusions: This rare and unique case highlights the importance that reproductive specialists should participate in the multidisciplinary consultation team to advise patients on the feasibility, effectiveness, and safety of fertility preservation before allogeneic hematopoietic stem cell transplantation. Although regarded as POI, pregnancy is hopeful if patient's antral follicle counts are visible under the transvaginal ultrasound.

Keywords: Allogeneic hematopoietic stem cell transplantation; Acute lymphoblastic leukemia; Premature ovarian insufficiency; Autologous oocyte; Intracytoplasmic sperm injection; Advanced reproductive age.

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Introduction

Hematopoietic Stem Cell Transplantation (HSCT) has long been established as an indispensable life-saving therapy for malignant and non-malignant hematological disorders. HSCT is one of the pathogenic factors for Premature Ovarian Insufficiency (POI). According to retrospective studies reported that the rates of POI range from 44 to 100% following female cancer survivor [1-4]. Clinical and demographic heterogeneity may account for the differences among the different study cohorts. With the improvement of HSCT, the number of long-term survivors has been increased yearly. However, subsequently infertility becomes a prominent concern for those survivors and contributes to depression and poor quality of life. Fertility preservation techniques, such as oocyte or embryo cryopreservation and ovarian tissue cryopreservation, may be the most possible way to promise fertility needs [5]. While owing to the acute presentation of patients' requiring urgent treatment, less time is allowed for women undergoing acute hematologic malignancies to proceed with fertility preservation. Figures indicate that only 20% of women who had become infertile secondary to cancer treatment had previously attempted fertility preservation [6]. Moreover, the preparative regimens for HSCT includes high-dose chemotherapy with or without irradiation, which can cause serious damage to female reproductive system, even lead to POI due to the massive destruction of ova and ovarian follicular elements [7].

Herein, we firstly report the rare case that a 42-year-old advanced age infertile woman in China had a live birth after undergoing Intracytoplasmic Sperm Injection (ICSI) obtained 41-year-old autologous oocyte and Frozen-thawed Embryo Transfer (FET), who developed POI after allogeneic HSCT following her diagnosis of acute lymphoblastic leukemia 23 years ago. She experienced 3 Controlled Ovarian Hyper Stimulation (COS) cycles and got her own viable 8CI embryo at her 41-year-old and had normally delivered a full-term healthy infant following frozen-thawed embryo transfer.

Case Report

A 40-year-old advanced age nulliparous Chinese female, presented for infertility counseling in December 2018 in our reproductive medicine center. She was diagnosed with acute lymphoblastic leukemia underwent allogeneic HSCT at the age of 19. She married at 28-year-old and had infertility for 12 years. Male partner was 46 years old on 2018, and his physical examination, chromosome karyotype and semen routine examination were normal.

In 2000, the female patient was diagnosed with acute lymphoblastic leukemia in 19-year-old. Subsequently, she received remission induction with VDLP chemotherapy for a total of 2 courses of treatment. And the regimen of VDLP chemotherapy referred to vincristine 2 mg intravenously on the 1st, 5th, and 8th days, daunorubicin 40 mg intravenously on the 1st and 2nd days, L-asparaginase 60 million iu intravenous infusion for 8 days from the 19th day, prednisone 60mg orally from the 1st to 28th day, then reduced to 45mg, and gradually reduced. Six subsequent intrathecal injections of methotrexate were used to prevent central nervous system leukemia. She underwent an allogeneic bone marrow transplant from her elder brother (HLA6/6 match, A+/A+). She then received a pretreatment regimen that included drugs such as cyclophosphamide, busulfan, semustine and antithymocyte globulin. Methotrexate and cyclosporine A were administered after transplantation to prevent acute Graft Versus Host Disease (GVHD). Six months after the operation, she received a total of 8 transfusions of peripheral blood stem cells from her elder brother. Nevertheless, During the 8th infusion, abnormal liver function occurred, which was considered as chronic liver rejection. Methylprednisolone and neostigmine were subsequently given anti-rejection and hepatoprotective therapy, and the patient's condition was subsequently stable.

She reported a menstruation history of menarche 13 years old, and regular 28 to 30 days cycles before HSCT. Secondary amenorrhea began six months following HSCT, at which time the patient's condition was stable and Hormone Replacement Therapy (HRT) was given. Since then, menstruation has started monthly. Although HRT was discontinued after one year of treatment, oligomenorrhea could be found. In 2018, her body mass index was 20.03 kg/m^2 and serum basal follicle-stimulating hormone (bFSH) level was 25.01 mIU/mL, serum basal luteinizing hormone (bLH) level was 5.86 mIU/mL, serum basal estrogen (bE_2) level was 11.96 pg/ml. Surprisingly, the Antral Follicle Count (AFC) revealed 3 in the left ovary and 1 in the right ovary according to transvaginal ultrasound. After five months later, the basal FSH was detected repeatedly (25.22 mIU/mL) and the Anti-Müllerian Hormone (AMH) measurement was 0.158 ng/ml. POI was definitely diagnosed for the patient. Moreover, she had been fully informed that the chances of getting pregnant by IVF-ET were extremely low. Family history of premature ovarian failure, exposure to harmful substances and ovarian surgery were not reported. In addition, both her chromosomes karyotype from genetic analysis of peripheral blood and her thyroid function were considered as normal. Fortunately, considering that the AFC could still be detected in the bilateral ovaries, the patient is advised to attempt Assisted Reproductive Technology (ART). Informed consent was given to patient with possible postoperative risks, such as egg retrieval failure, no viable embryo for transfer, low pregnancy rate, high miscarriage rate, and possible reproductive toxicity of chemotherapy drugs, etc. This case was approved by the ethics committee of Nanfang Hospital.

Materials and methods

For the reason that the donor oocytes are hard to obtain and they were keen to have a try with autologous gamete. Prior to assisted reproductive technology, comprehensive assessment had been taken by hematologist and the patient's condition was under control. We decided to accumulate more embryos via several COS cycles because of her advanced age. The first cycle was attempted in April 2019 in her 41 years. A follicle with a diameter of 15mm was observed under transvaginal ultrasound on the 15th day of the menstrual cycle when the patient was admitted. We administered 150 IU human menopausal gonadotropin (HMG,150 IU) and 0.25 mg GnRH antagonist (Cetrorelix, Merck Serono, Germany, specification 0.25 mg) for two days. After that, blood testing showed that LH had increased to 41.05 mIU/ mL and P to 0.433 ng/ mL. Further, the 250 μg recombinant Human Choriogonadotropin alfa Solution (Ovidrel, Merck Serono, Germany, specification:250 μg:0.5 ml) was immediately administered for the trigger of final oocyte maturation. However, the cycle was finally canceled due to premature ovulation found on the day of oocyte retrieval.

In the second cycle, one antral follicle was detected under transvaginal ultrasound scan on the second day of menstruation. The patient was administered with 150 IU highly purified FSH (HP-FSH; Lishenbao 150 IU, Livzon Pharmaceuticals, China) for 4 days at the beginning of ovarian stimulation. The GnRH

antagonist protocol were prescribed. The total dose of gonadotropins was 1350 IU for 9 days. In addition, we added 4.5 IU of recombinant human growth hormone (Serzin, specification: 4.5IU) throughout the course for 13 days. Subsequently, a follicle with a diameter of 19mm was detected, oocyte maturation was triggered with a first dose of GnRH-a (Triptorelin acetate, Decapeptyl, Ferring Pharmaceuticals, Israel, specification:0.25mg) and recombinant Human Choriogonadotropin alfa Solution for Injection of 250 μg (Ovidrel, Merck Serono, Germany, specification:250 μg:0.5 ml). On the day of trigger, her E_2 was 323.2 pg/mL, P was 0.196 ng/mL, and only 1 follicle were visible, of which were 19 mm. The oocyte was retrieved under transvaginal ultrasound guidance at 35-36 h after injection of HCG. And then, ICSI was performed and developed into an 8CI embryo with fragmentation rate of 5% on day 3.

In the third cycle, the GnRH antagonist regimen was followed as mentioned above. Recombinant follicle-stimulating hormone (rFSH; Gonal F 300 IU, Merck Serono, Italy) was started with 300IU and the total dose of gonadotropins was 3600 IU for 12 days. Then, only 1 follicle with a diameter of >16mm was obtained during the ovarian retrieval and sperm was injected into the oocyte from metaphase II stage via ICSI. However, no cleavage was observed in the day 1 and day 2 after fertilization and the oocyte was discarded subsequently.

In November 2019, the patient underwent fourth cycle of ovulation stimulation with mild stimulation regimen. Clomiphene Citrate tablets was taken in 150 mg for 4 days until the trigger. On the day of trigger, her E_2 was 306.2 pg/mL, P was 0.172 ng/mL, and only 1 follicle of >15 mm were visible. However, no oocyte was obtained on the day of ovarian retrieval. In March 2020, the FSH was 97.34 mIU/mL and AMH was 0.016 ng/mL. Repeated transvaginal ultrasound monitoring showed no AFC in the bilateral ovaries.

The patient was informed that her ovarian function might fail to the end stage, and the possibility of subsequent successful ovulation induction was relatively low. The patient understood and asked for transferring the only remaining viable embryo. In April 2020, when she was about to be 42, HRT-FET was scheduled while the remaining embryo was developed into 6CI embryos after thawing and continued to be cultured to morula. On the day of transplantation, the thickness of endometrium was 1.2 cm, and strong echoes was found in the morphology of endometrium.

Results

The patient totally underwent 3 cycles of oocyte retrieval, only 2 eggs were obtained at 41-year-old, and formed only one viable 8CI embryo. Confirmed pregnancy in the light of serum β-HCG was 290.4 mIU/mL after 14 days of FET. Clinical pregnancy was confirmed when the gestational sac was seen inside of the uterus by transvaginal ultrasound examination after 4 weeks of FET. No abnormalities were found while the patient performed amniocentesis, fetal chromosome and gene chip examination during pregnancy. The patient was closely monitored during her antenatal period and postpartum period. The blood glucose was well controlled although gestational diabetes mellitus was diagnosed as A1 level. She was admitted at 38 weeks and 5 days for monitoring blood pressure increased for 3 days. The maximum longitude of amniotic fluid was 1.2 cm and amniotic fluid index was 3.2 cm.

Considering that the risks of gestational hypertension and oligohydramnios, vaginal delivery was induced by oxytocin at 39+3 weeks of gestation, and a healthy male baby weighing 3,140 g was delivered after lateral perineal incision. Apgar scores were 10 at 1, 5 and 10 minutes respectively. The patient had a hemorrhage of 685 ml 24 hours after delivery and presented with symptoms such as chills and fever. The patient was diagnosed with severe anemia after monitoring HGB 56 g/L and received an infusion of 2u homologous erythrocyte to correct anemia. The newborn was hospitalized in the neonatology department for 7 days for transient shortness of breath due to infection and was discharged after his condition improved. The mother and baby are recovering well and no complications have been found after follow-up visiting.

Table 1: Clinical and biological characteristic of the patient included in the study.

Characteristic	No. 1 period	No. 2 period	No. 3 period	No. 4 period	No. 5 period
Medication regimen	GnRH-ant	GnRH-ant	GnRH-ant	MS	HRT
ART regimen	IVF	ICSI	ICSI	ICSI	FET
Gn duration(days)	2	9	12	-	-
Total dose of Gn (IU)	300	1350	3600	-	-
FSH (mIU/mL) on trigger day	36.18	44.17	65.61	36.45	-
LH (mIU/mL) on trigger day	41.05	15.14	26.02	22.41	-
Progesterone (ng/mL) on trigger day	0.433	0.196	0.212	0.172	-
E_2 (pg/mL) on trigger day	124.4	323.2	283	306.2	-
Endometrium thickness (mm)	-	8	6	7	12
No. of oocytes retrieved	-	1	1	0	-
No. of frozen embryos on day 3	-	1	0	0	-
No. of available embryos	-	1	0	0	-
Transfer embryo morphology	-	-	-	-	Morula

Abbreviations: GnRH-ant: Gonadotropin Releasing Hormone antagonist; MS: Mild Stimulation; HRT: Hormone Replacement Therapy; ART: Assisted Reproductive Technology; IVF-ET: In Vitro Fertilization-Embryo Transfer; ICSI: Intracytoplasmic Sperm Injection; FET: Frozen-Thawed Embryo Transfer; Gn: Gonadotropin; FSH: Follicle-Stimulating Hormone; LH: Luteinizing Hormone; E_2: Oestrogen.

Discussion

Premature Ovarian Insufficiency (POI) and infertility are the most concerned issues after allogeneic Hematopoietic Stem Cell Transplantation (HSCT) in young women [8]. Low pregnancy rate was established for those survivors who underwent chemotherapy, pelvic radiotherapy. Salooja N et al conducted a questionnaire in 199 centers involving 37362 transplant patients, of whom only 232 were pregnant (0.6%) [9]. The most of women who undergo HSCT rely on fertility preservation techniques, including In Vitro Fertilization (IVF) and embryo cryopreservation, oocyte cryopreservation or ovarian tissue cryopreservation, and a minority of survivors choose egg donation IVF-ET to achieve fertility aspirations [10]. In this case, a 42-year-old advanced age woman developed POI after allogeneic HSCT following her diagnosis of acute lymphoblastic leukemia 23 years ago. She successfully conceived with her own only oocyte obtained at 41-year-old by means of ICSI and FET. Only one viable 8CI embryo was transferred under the treatment of HRT-FET, resulting in a pregnancy and full-term vaginal delivery at 39 weeks and 3 days of a healthy male baby weighing 3,140 g. Such a unique case is rarely reported, which should arouse our profound attention and reflection on the management of postoperative complications in HSCT survivors.

Various preoperative myeloablative pretreatment schemes are adopted for allogeneic HSCT patients. And the most classic chemotherapy regimen is cyclophosphamide with or without Total Body Irradiation (TBI). Patients with TBI should also be informed of the increased risk of miscarriage, preterm birth and low birth weight in pregnancy due to radiation exposure to the pelvic uterus [9,10]. Studies have shown that the prepubertal uterus is more susceptible to radiation exposure than after puberty [11]. Moreover, radiotherapy is known to be directly toxic to oocytes and pretreatment regimen with TBI resulted in a much higher incidence of ovarian dysfunction than chemotherapy alone [12,13]. The pretreatment scheme did not involve TBI in our case, which was one of the improved schemes with reduced intensity. Hence, this may be one of the favorable conditions for the patient to maintain ovarian function for 23 years after myeloablative preconditioning.

Determinants of the effect of chemotherapy on ovarian reserve include age, drug type, dosage, treatment time, administration method, baseline ovarian reserve prior to chemotherapy and actual treatment regiments. Chemotherapy-related alkylating agents are risk factors for ovarian dysfunction, particularly chlorambucil, cyclophosphamide, melphalan, busulfan and procarbazine which have distinctly toxic damage to ovary [14]. Chemotherapeutic drugs cause decreased ovarian function by inducing accelerated depletion of the primordial follicular pool, ovarian cortical fibrosis, ovarian atrophy and decreased ovarian blood flow [15]. The loss of the primordial follicle pool in a quiescent state is due to the fact that cyclophosphamide can activate primordial follicles, so that they can be recruited to primary or secondary follicles and then suffer cytotoxic damage [16]. Therefore, the degree of ovarian function impairment should be preliminarily judged by reproductive specialists according to the history of radiotherapy and the intensity of chemotherapy regimen when receiving patients after HSCT.

It is well known that age is one of the most significant concerns for reproductive specialists. Advanced maternal age over 40 years is accompanied by decreased ovarian reserve and adverse pregnancy outcomes such as spontaneous miscarriage, chromosomal abnormalities and preterm birth [17,18]. It has also been proved that the age of chemotherapy is one of the risk factors for decreased ovarian function, and the older the age, the higher the probability of permanent amenorrhea after chemotherapy treatment [14]. In addition, the remaining primordial follicle pool may retain a relatively large number of unactivated primordial follicles. Since the patient underwent HSCT in puberty, this may be one of the important reasons to interpret the delayed ovarian failure. Bresters et al. reported that the cumulative incidence of ovarian insufficiency was significantly different in the three pubertal stages at HSCT with the highest incidence in the post-pubertal females (79%), followed by pubertal females (67%) and the lowest incidence in pre-pubertal females (45%) [19]. Unfortunately, this study did not follow all patients up to age 40, and the actual incidence of POI should be higher than this statistic. The patient in our case was 13 years old when menstruating and underwent myeloablative chemotherapy before HSCT at the age of 19. She was a post-adolescent female, but she was a relatively young woman of childbearing age. There may be more follicles in her original follicular pool that were not damaged by chemotherapy, which may lead to follicular growth 23 years after HSCT. Besides, it was not determined whether the patient was in a high response to ovarian stimulation prior to HSCT.

The patient cured after HSCT, but turned to the reproductive center for several years due to infertility. Some fertility specialists refused to provide ART considering that the chemotherapy and advanced maternal age may be result in reproductive toxicity, risk of increasing aneuploidies, other pregnancy-related complications and extremely low live birth rates and risk of relapse in ALL [20]. It is also worth paying great attention to concern that cytotoxicity of chemotherapeutic drugs may cause oxidative damage and genetic mutations to germ cells, resulting in deformities of progeny. The safe time interval between discontinuing chemotherapy drugs and harvesting eggs remains unknown [21]. It has been reported that the rate of birth malformations increased in animal models after cyclophosphamide treatment, and the malformation rate was highest in pregnancy immediately after cyclophosphamide treatment [22]. But in multiple reports of reproductive outcomes for cancer survivors, there was no increase in the rate of miscarriage, birth defects, single-gene defects, Down syndrome or Turner syndrome [23-25]. It is assumed that chemotherapy has the most serious impact on mature oocytes and the least impact on primitive follicles, and it takes 10-13 months from the growth and development of primitive follicles to mature follicles [26]. Therefore, oocytes have a greater risk of teratogenesis within 13 months, while the longer the time after chemotherapy, the less possibility of teratogenesis. However, there is a lack of strong evidence to support this inference, so the possible teratogenic risk should be fully informed before helping such patients have children. In this case, no obvious malformations were found in the neonate, but long-term follow-up is required for the offspring's growth, development and neurological function. For patients with POF, HRT treatment should be given to manage their long-term health, and for those who still have fertility requirements, ovum donation IVF is recommended.

Conclusion

This rare and unique case that we firstly reported highlights the importance that reproductive specialists should participate in the multidisciplinary consultation team to advise patients on the feasibility, effectiveness, and safety of fertility preservation before HSCT. For patients with acute leukemia who do not have

enough time for fertility preservation, their ovarian function should be assessed as soon as possible after their condition is stable and they should be actively assisted with pregnancy, and they should be fully informed of the possible teratogenic risk. Although regarded as POI, pregnancy is hopeful if patient's antral follicles are visible under the transvaginal ultrasound.

Declarations

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Attestation statements: The subjects in this case have not concomitantly been involved in other randomized trials. In addition, Data regarding any of the subject in the study has not been previously published unless specified. And Data will be made available to the editors of the journal for review or query upon request.

Capsule: This rare and unique case highlights the importance that reproductive specialists should participate in the multidisciplinary consultation team to advise patients on the feasibility, effectiveness, and safety of fertility preservation.

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