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Case Report

Spontaneous pregnancy after prepubertal haematopoietic cell transplantation

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ABSTRACT

Spontaneous pregnancy after haematopoietic cell transplantation (HCT) is rare due to an increase incidence of premature ovarian failure resulting from pre-transplantation conditioning regimes. Increased number of long term survival of HCT patients has brought forth their fertility into focus. In this article, we reported a 34 years old woman who underwent HCT at prepubertal age and had a spontaneous pregnancy. In addition, we reviewed literature on fertility outcome in HCT survivors and the associated risk factors.

Keywords: Hematopoietic cell transplantation, Prepubertal, Spontaneous pregnancy

INTRODUCTION

HCT is curative for various haematological diseases such as leukaemia, lymphoma, thalassemia, sickle cell anaemia and aplastic anaemia. Improved transplant outcome and better supportive care have increased the long-term survival of HCT patients. This has also surfaced quality of life issues including fertility.

Prior to HCT procedure, a conditioning regimen is necessary to provide adequate immunosuppression and prevent rejection of the transplanted graft. These include chemotherapy and irradiation which cause germ cell injury and gonadal dysfunction leading to infertility. Conditioning regimes can be myeloablative or non-myeloablative regimes. A myeloablative (MA) regimen aims to destroy all the cells in the bone marrow prior to new hemotopoietic stem cell infusion. Non myeloablative (NMA) regimens cause minimal cytopenia (but significant lymphopenia). They do not require cell support and focus on immunosuppression to allow engraftment. Single or combination agents used for myeloablation are more toxic than non-myeloablative

regimes.¹⁻⁴ Limited studies have been done to compare fertility outcome of both regimes.⁵ Rates of conception in women among the HCT survivors have ranged from 0.6-5.5 %.^{6,7} They had a 36-fold lower conception rate compared to their siblings.⁶ The fertility prognosis varies with pre-transplant conditioning regimes.⁸

CASE REPORT

A 34 years old nulliparous woman with a history of aplastic anaemia came to our subfertility clinic after trying to conceive for 2 years. She was diagnosed to have severe aplastic anaemia at 7 years of age and had an allogeneic bone marrow transplant 4 years later.

Prior to the transplant, she was conditioned with cumulative intravenous cyclophosphamide 6.5g and total lymphoid irradiation 750 cGy in 1 fraction. Post operatively, she was given cyclosporin A and methotrexate for immunosuppression. She was followed up by haematology for a few years and discharged without any long-term medication. She attained spontaneous puberty 2 years later at 13 years of age.

Thereafter she had regular menses every 21 days. She was married for 6 years and consulted us for fertility. At fertility workup, her husband's semen was unremarkable. Her FSH was 12.5 U/L with a low antral follicle count of 8. She was offered in vitro fertilisation (IVF) in view of her low ovarian reserve and underwent a hysteroscopy polypectomy for a 0.8 cm endometrial polyp. However, she conceived immediately in the following cycle while awaiting IVF workup. In view of the interesting presentation, we reviewed the literature over the past 20 years to identify fertility outcome after HCT.

DISCUSSION

HCT is known to reduce fertility in long-term survivors. The European Group for Blood and Marrow Transplantation (EBMT) study reported that the overall pregnancy rate after bone marrow transplant was 0.6%. Data from Center for international blood and marrow transplant research (CIBMTR) showed a 5.5% conception rate among HCT survivors compared to their siblings (70% conception rate). Overall HCT survivors had lower prevalence of conception.^{6,7}

Radiation-based conditioning in HCT usually refers to total body irradiation (TBI). Patients who undergo total body irradiation have a higher prevalence of infertility compared to others (odds ratio 3.32, $P=0.003$).⁶ A minority of HCT survivors recover from gonadal function and rarely get pregnant.^{9,10} The dosage of radiation affects the conception rate. An ovarian dosage of 15 Gy can lead to irreversible infertility even in prepubertal women.¹¹ A TBI dose of 12 Gy can cause ovarian damage in all the patients over 10 years old and half of the patients before 10 years old.¹²

Total lymphoid irradiation (TLI) was first introduced in 1977 to minimise complications from TBI and facilitate graft uptake. Limited studies have been done on the effect of total lymphoid irradiation on subfertility. Charles et al compared short-term high-dose cyclophosphamide combined with single-dose total lymphoid irradiation (Group 1) versus high-dose chemotherapy plus single-dose total body irradiation (Group 2). Around 50% of the patients in Group 1 continued to have regular menses and normal gonadotropin levels, 36 months post-BMT, while all the patients in Group 2 had elevated plasma levels of FSH and LH over a 17 to 45-month period of time. None of the patients in Group 2 menstruated after undergoing HCT. To our knowledge, there are no publications on the conception rate in patients who undergo chemotherapy with total lymphoid irradiation.⁸

Studies had showed the treatment with cyclophosphamide in a cumulative dose of 12 to 25 g increases the risk of amenorrhea (ranged 27-60%).¹³⁻¹⁸ More than 80% of these patients had premature ovarian failure. Risk factors for sustained amenorrhea are patient's age when cyclophosphamide started and cumulative dosage of cyclophosphamide. Huong et al and Mok et al reported

that with the use of 12 g and 18 g cumulative dose of cyclophosphamide respectively had resulted in 10 % risk of amenorrhea in patients less than 30 years of age compared with 60 % in patients above 40 years old.^{11,18} The risk of amenorrhea is low if the patient received a cumulative cyclophosphamide dose of less than 10 g.¹⁹ The route of administration is not related to the risk of amenorrhea.²⁰

Nonmyeloablative regimes are more likely to preserve fertility compared to myeloablative regimes as the dosage of TBI and chemotherapy is lower.^{10,21,22} In addition, recent data have shown that similar outcomes are possible between nonmyeloablative and myeloablative regimes among HCT survivors in certain disorders such as lymphoma, chronic lymphocytic leukaemia, acute myelogenous leukaemia and myelodysplastic syndrome.²³⁻²⁵ Therefore, fertility outcome with nonmyeloablative regimes warrants further research and study.

The patients' age at the time of bone marrow transplant could influence the recovery of ovarian function. Patient underwent HCT at a younger age have better prognosis in preserving their fertility. Sander's et al reported that 32 out of 43 women who had cyclophosphamide alone as a preconditioning regime subsequently had normal gonadotrophin levels and menstruation but return of ovarian function was less likely over the age of 26 years.¹⁰ Alison et al reported that the pregnancy rate was markedly reduced when bone marrow transplant occurred at the later age (>20 years old).⁵ Matsumoto et al concluded that younger girls had a higher incidence of menarche than older girls (Mean (SD), 7.2 (0.5) versus 11.1 (1.7) years). Basal FSH began to rise to menopausal concentrations after 10 years of age, and girls who did not experience menarche had a sustained rise in FSH concentrations. Among those with a raised FSH, 5 girls experienced menarche while serum FSH values were decreasing and 4 girls achieved menarche while FSH remained elevated.²⁶

Several studies have reported pregnancy outcomes among female HCT survivors. Carter et al reported no significant increase in miscarriage and stillbirth rate in these patients compared to their siblings.⁶ However there was no comprehensive analysis to correlate each conditional regime toward the pregnancy outcome. Sanders et al reported that female HCT survivors who received TBI had a 38% miscarriage rate after 10.0 Gy single exposure or 12-14.0 Gy fractionated exposure. There were no miscarriages among patients who had TBI less than 5-8 Gy. Furthermore, patients who received cyclophosphamide had a 7% miscarriage rate.²⁷ There is no clear data to show that HCT increased the risk of preterm labour and low birth weight infants.^{21,22,28} Further studies are required for appropriate conclusions to be drawn. There is no increased risk of congenital abnormality among the children of HCT survivors.^{21,22,27,28}

CONCLUSION

In conclusion, patients who received TBI have a low likelihood of pregnancy. TBI patients are more prone to an increased miscarriage rate depending on the quantum of radiation. Our patient received total lymphoid irradiation and cyclophosphamide (cumulative dose of 6.5g) as a conditioning regime and had a spontaneous pregnancy. This is probably due to the nonmyeloablative nature of her regimen. Limited studies have reported pregnancy and miscarriage rate among patients who had received this combination. Further studies are necessary to compare various conditioning regimes and elucidate the optimal one for the treatment of haematological disorders requiring HCT with a better fertility outcome.

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