Motherisk Update

Pregnancy after stem cell transplantation

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ABSTRACT

QUESTION A married woman under my care underwent successful bone marrow transplantation as part of treatment for a malignancy. She wishes to start a family. What are her chances? Are there risks?

ANSWER Success in becoming pregnant after stem cell transplantation depends on such factors as cumulative doses of chemotherapy and radiation and mother's age at time of transplant. There is increased risk of prematurity, low birth weight, and spontaneous abortion. Pregnancy should be managed as high risk.

RÉSUMÉ

QUESTION Une femme mariée que je soigne vient de subir avec succès une transplantation de la moelle osseuse dans le contexte d'un traitement contre le cancer. Elle envisage de commencer une famille. Quelles sont ses chances et quels sont les risques?

RÉPONSE Réussir à devenir enceinte après une transplantation de cellules souches dépend de facteurs comme les doses cumulatives de chimiothérapie et de rayonnement, ainsi que l'âge de la future mère au moment de la transplantation. Il y a un risque accru d'accouchement prématuré, de faible poids à la naissance et d'avortement spontané. La grossesse devrait être prise en charge comme étant à risque élevé.

An increasing number of young women suffering from leukemia and other malignant and nonmalignant disorders are being cured by stem cell transplantation (SCT). Improved survival introduces the long-term consequences of SCT, including fertility issues.

Pregnancies following SCT are still rare. The options for conceiving include spontaneous conception and in vitro fertilization with donated or the mother's own eggs (with embryo cryopreservation before or after chemotherapy).[1] Harvesting and freezing unfertilized eggs is technically difficult and frequently unavailable.[1]

Most pretransplant conditioning protocols for SCT include alkylating agents, irradiation, or both. Either of these options can injure germ cells and cause infertility. Thus, almost all women become infertile immediately after SCT due to damage to the ovaries.[2]

Some women become permanently infertile; others recover fertility. Recovery of ovarian function and fertility has been shown to depend on several factors. The most important risk factors for development of ovarian failure are advanced age at time of first treatment and the number of cycles with alkylating agents and irradiation.[3]

All alkylating agents have toxic effects on the ovaries. These effects have been mostly documented with cyclophosphamide.[4] Irradiation doses as low as 4 Gy destroy about 50% of oocytes.[5] Use of alkylating agents combined with irradiation below the diaphragm causes more pronounced damage.[6-8] Women more often recover fertility if their irradiation regimens do not affect the whole body and if they are younger than 25 years.[1]

In allogeneic SCT, recovery of ovarian function ranges from 14% to 24%,[9-11] and the interval from SCT to first spontaneous menstruation ranges from 21 to 87 months (median 49 months).[12] Recovery rates as high as 84% have been reported among patients with favourable predictors. These patients were young,

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and none received total body irradiation as part of transplant conditioning.[10] Rates of recovery of ovarian function after autologous SCT are expected to be higher than after allotransplantation, because autologous SCT does not require subsequent immunosuppressive therapy, and recipients do not experience graft-versus-host disease. A study of 17 women who underwent autologous SCT showed that five (29%) recovered their ovarian function and that the recovery rate for women younger than 25 years was 79%.[2]

In a larger study, 32 out of 110 women who recovered ovarian function became pregnant at a median of 8.5 years after allotransplantation.[13] Another study found that pregnancy can occasionally be achieved in women with non-Hodgkin lymphoma, whether or not they have undergone high-dose therapy with autologous SCT.[14] The pregnancy rate was not lower among women treated with high-dose chemotherapy, despite a cumulative dose of cyclophosphamide of 10 800 mg/m^2. Only the youngest patients became pregnant; no pregnancy was observed among women who were older than 29 years when diagnosed with a non-Hodgkin lymphoma.[14]

A recent study evaluated pregnancy outcome among 113 women after SCT[15] and found that 85% of pregnancies resulted in live births. Only 0.82% of the children had severe anomalies, a rate not higher than that reported in the general population. Among allograft recipients, 42% had cesarean sections (compared with 16% in the general population), 20% had preterm deliveries (compared with 6% in the general population), and 23% had low birth weight infants (compared with 6% in the general population). The authors recommended that pregnancies in patients who received allografts and total body irradiation should be treated as high risk.[15] Other researchers reported an increased risk of spontaneous abortion in women treated with SCT and total body irradiation.[13]

An important association was found between pregnancy and a relatively high rate of relapse of chronic myeloid leukemia after SCT. Suppression of the graft-versus-leukemia effect during pregnancy was suggested as the mechanism of relapse.[16,17]

In the future, alternative chemotherapeutic regimens with lower doses of alkylating agents need to be investigated for women who wish to become pregnant after SCT, at least until oocyte or ovarian cryopreservation becomes routinely available.

References

1. Lipton JH, Virro M, Solow H. Successful pregnancy after allogeneic bone marrow transplant with embryos isolated before transplant. *J Clin Oncol* 1997;15:3347-9.
2. Schimmer AD, Quatermain M, Imrie K, Ali V, McCrae J, Stewart AK, et al. Ovarian function after autologous bone marrow transplantation. *J Clin Oncol* 1998;16:2359-63.
3. Apperley JF, Reddy N. Mechanism and management of treatment-related gonadal failure in recipients of high dose chemoradiotherapy. *Blood Rev* 1995;9:93-116.
4. Chabner BA, Allegra CJ, Curt GA, Clendeninn NJ, Baram J, Koizumi S, et al. Antineoplastic agents. In: Hardman JG, Limbird LE, editors. *Goodman and Gilman's the pharmacological basis of therapeutics*. 9th ed. New York, NY: McGraw-Hill; 1996. p. 1233-87.
5. Damewood MD, Grochow LB. Prospects for fertility after chemotherapy or radiation for neoplastic disease. *Fertil Steril* 1986;45:443-59.
6. Aisner J, Wiernik PH, Pearl P. Pregnancy outcome in patients treated for Hodgkin's disease. *J Clin Oncol* 1993;11:507-12.
7. Li FP, Gimbrere K, Gelber RD, Sallan SE, Flamant F, Green DM, et al. Outcome of pregnancy in survivors of Wilms' tumor. *JAMA* 1987;257:216-9.
8. Ortin TT, Shostak CA, Donaldson SS. Gonadal status and reproductive function following treatment for Hodgkin's disease in childhood: the Stanford experience. *Int J Radiat Oncol Biol Phys* 1990;19:873-80.
9. Cohen A, Van-Lint MT, Lavagetto A, Chiodi S, Spinelli S, Bacigalupo A, et al. Pubertal development and fertility in children after bone marrow transplantion. *Bone Marrow Transplant* 1991;8(Suppl 1):16-20.
10. Sanders JE, Buckner CD, Amos D, Levy W, Appelbaum FR, Doney K, et al. Ovarian function following marrow transplantation for aplastic anemia or leukemia. *J Clin Oncol* 1988;6:813-8.
11. Chatterjee R, Mills W, Katz M, McGarrigle HH, Goldstone AH. Prospective study of pituitary-gonadal function to evaluate short-term effects of ablative chemotherapy or total body irradiation with autologous or allogenic marrow transplantation in post-menarcheal female patients. *Bone Marrow Transplant* 1994;13:511-7.
12. Spinelli S, Chiodi S, Bacigalupo A, Brasca A, Menada MV, Petti AR, et al. Ovarian recovery after total body irradiation and allogeneic bone marrow transplantation: long-term follow up of 79 females. *Bone Marrow Transplant* 1994;14:373-80.
13. Sanders JE, Hawley J, Levy W, Gooley T, Buckner CD, Deeg HJ, et al. Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. *Blood* 1996;87:3045-52.
14. Brice P, Haioun C, Andre M, Gisselbrecht C. Pregnancies after high-dose chemotherapy and autologous stem cell transplantation in aggressive lymphoma. *Blood* 2002;100:736.
15. Salooja N, Szydlo RM, Socie G, Rio B, Chatterjee R, Ljungman P, et al. Pregnancy outcomes after peripheral blood or bone marrow transplantation: a retrospective survey. *Lancet* 2001;358:271-6.
16. Atkinson HG, Apperley JF, Dawson K, Goldman JM, Winston RM. Successful pregnancy after allogeneic bone marrow transplantation for chronic myeloid leukemia. *Lancet* 1994;344:199.
17. Rio B, Cymbalista F, Ramond S, Hunault M, Zittoun R. Does pregnancy after alloBMT suppress GVL effect? [abstract]. *Bone Marrow Transplant* 1995;15:S61.

MOTHERISK

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. Drs Schechter and Finkelstein are members and Dr Koren is Director of the Motherisk Program. Dr Doyle is Director of the Bone Marrow Transplant Unit at the Hospital for Sick Children. Dr Koren, a Senior Scientist at the Canadian Institutes of Health Research, is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation and holds the Ivey Chair in Molecular Toxicology at The University of Western Ontario.

Do you have questions about the safety of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at (416) 813-7562; they will be addressed in future Motherisk Updates.

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