Fertility recovery and pregnancy after allogeneic hematopoietic stem cell transplantation in Fanconi anemia patients

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ABSTRACT

Reduced fertility is one clinical manifestation among other well known Fanconi anemia features. Most recipients of allogeneic hematopoietic stem cell transplantation suffer from secondary infertility owing to gonadal damage from myeloablative conditioning. In order to evaluate the rate of pregnancy in Fanconi anemia transplanted patients, we performed a retrospective analysis of female patients transplanted in 15 centers from 1976 to 2008. Among 578 transplanted Fanconi anemia patients, we identified 285 transplanted females of whom 101 patients were aged 16 years or over. Ten became pregnant (4 twice). Before hematopoietic stem cell transplantation all had confirmed Fanconi anemia diagnosis. Median age at transplantation was 12 years (range 5-17 years). Conditioning regimen consisted of cyclophosphamide with or without irradiation. During follow up, 5 of 10 patients presented signs of ovarian failure. Among those, 2 patients spontaneously recovered regular menses, and 3 received hormonal replacement therapy. Pregnancy occurred from four to 17 years after hematopoietic stem cell transplantation. Three patients had preterm deliveries, one patient had a hysterectomy for bleeding. All 14 newborns had normal growth and development without congenital diseases. In conclusion, recovery of normal ovarian function and a viable pregnancy is a realistic but relatively rare possibility even in Fanconi anemia patients following hematopoietic stem cell transplantation. Mechanisms of fertility recovery are discussed.

Key words: pregnancy, Fanconi anemia, bone marrow transplantation.

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Introduction

Fanconi anemia (FA) is a rare autosomal recessive disorder that belongs to the group of chromosomal instability syndromes. FA cells of all organ tissues are hypersensitive to DNA cross-linking agents and to oxygen, and have cell cycle abnormalities. Its clinical features include progressive bone marrow failure, skeletal and urogenital malformations, skin hyperpigmentation, increased susceptibility to malignancy and reduced fertility.[1,2] As base-line, in non-transplanted FA patients who reach adult age, the rate of successful pregnancy has been estimated at 15%.[3] Hematopoietic stem cell transplantation (HSCT), using an adapted attenuated conditioning regimen, represents the only curative therapy capable of restoring normal hematopoiesis in patients with FA. In FA, the conditioning has been reduced because of the toxic effect of alkylating agents.[4] For this reason, most centers use low-dose cyclophosphamide with or without irradiation assuming that this is the equivalent of a myeloablative conditioning considering the DNA repair defect related to the genetic mutation.[5] In order to describe fertility in female patients after transplant, we designed a multicenter retrospective analysis of posttransplant pregnancy in FA patients.

Design and Methods

Fifteen transplant centers from 10 different countries participated in this survey. Centers that reported pregnancies after transplant were asked to fill in a specific disease form and the MED-B EBMT form including detailed information on diagnosis, transplant procedure, gynecological and obstetrics follow up.

From 1976 to 2008, these 15 centers had transplanted 578 FA patients. Among them, there were 285 female patients but only 101 reached at least 16 years and were potentially at risk of pregnancy. The total number of reported pregnancies was 14 and we present the detailed case reports of 10 patients from 8 different centers, since 4 of them became pregnant twice after HSCT. Four patients have been previously reported (patients 4, 5, 6 and 9).[6-8]

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Results and Discussion

Patient characteristics are summarized in Table 1. Their median age at diagnosis was eight years (range 4-17). They presented with different phenotypes of the disease: some had only classical hallmarks such as *café au lait* spots and thumb abnormalities but others presented more severe abnormalities such as deafness, congenital hip dysplasia and trachea-esophageal fistula. All diagnoses were confirmed by increased chromosomal breakage following exposure to DNA cross-linking agents such as mitomycin C or diepoxybutane (DEB). Mutation analysis was not performed at that time.

One of our 10 patients could be considered to have an extensive malformation syndrome, defined by the presence of abnormalities in at least 3 different sites, involving the head, limbs, gastro-intestinal, urogenital and cardiovascular abnormalities. Skin abnormalities were not included in this classification.

All patients presented with pancytopenia and non-severe or severe marrow aplasia. Five had received previous treatment with androgens and corticosteroids, with temporary or no response before transplant and were heavily transfused.

At transplantation, the median age of patients was 12 years (range 5-19). Donors were HLA matched siblings in 8 cases and unrelated matched bone marrow in 2 (patients 4 and 9). Conditioning is described in Table 1; most patients received low-dose cyclophosphamide and 4-6 Gy irradiation involving the ovaries, 3 patients received high-dose cyclophosphamide without irradiation. Graft *versus* host disease (GVHD) prophylaxis consisted of cyclosporine and methotrexate or cyclosporine alone in 2 cases. Median follow up (FU) was 14 years (range 9-20). All patients engrafted with full long-term hematologic reconstitution. Only one patient developed grade II acute skin GVHD responsive to prednisone. Finally, no patient with pregnancy had severe chronic GVHD.

Regarding their gynecological follow up, 5 patients had spontaneous puberty development after transplant. Among those 5 patients, 4 had received 4-6 Gy TBI or TAI. The other 5 patients were diagnosed with ovarian failure characterized by amenorrhea, high levels of follicle-stimulating hormone and luteinizing hormone, and low levels of oestradiol. One patient also had uterine and ovarian atrophy and another presented with symptomatic menopause. However, only 3 received hormonal replacement therapy (HRT) with estrogens and progestagens for 2-4 years before developing regular menses and becoming pregnant. Two patients recovered fertility without any treatment.

Their median age at pregnancy was 21 years (range 18-23) and the median time from transplant to pregnancy was eight years (range 4-16). During pregnancy, the patients were followed regularly with blood counts, hepatic, cardiac and renal function tests; all were normal except for one patient who developed preeclampsia with hypertension and transient renal failure which resolved after delivery. No spontaneous abortion was observed among these 10 patients. Term delivery was observed in 11 cases. Three patients had preterm delivery, and 2 had a cesarean section. One patient had preeclampsia at 27 weeks. Only one post partum complication was observed with an uncontrolled uterine hemorrhage resulting in hysterectomy.

There were 14 live births (9 males and 5 females). The 27-week premature baby weighed 870 g at birth and was kept in an intensive care unit during her first 45 days of life. Ultimately her development was normal. Currently, they are all healthy children with normal growth and development without congenital abnormalities and normal blood cytogenetics.

The patients did not receive any additional treatment after delivery and their hematologic status remained stable during and after pregnancy. Unfortunately, one patient presented with tongue and esophagus squamous cell carcinoma and died as a result of this malignant complication 20 years after transplant and 15 years after her first pregnancy. The other 9 mothers are alive and well.

Pregnancy following HSCT after myeloablative conditioning is considered to be a rare event.[9-14] In the largest multicenter European retrospective study on pregnancy outcomes after transplant, 232 out of 37,362 autologous and allogeneic HSCT patients (0.6%) conceived after HSCT.[9] In Seattle, among 1,522 disease free survivors following marrow transplant between August 1971 and January 1992, 41 female patients and partners of 35 male patients had 146 pregnancies after transplant.[10] The dose of irradiation required to destroy 50% of immature oocytes has been estimated at 2 Gy[15]. Reduced ovarian volume and low inhibin B and anti-Mullerian hormone concentrations in survivors with regular menses may be markers of incipient ovarian failure.[15] In addition, uterine damage manifested by impaired growth and blood flow is a likely consequence of pelvic irradiation.[11] However, the true incidence of pregnancy and pregnancy-related complications after transplantation are unknown.[12-14]

Fanconi anemia patients posttransplant are supposed to have an even lower probability of fertility recovery compared to other transplant groups and three distinct factors can be incriminated: hypergonadotropic hypogonadism related to FA status, radiotherapy and greater toxicity from chemotherapy in cells presenting increased sensitivity to DNA damage. However, several isolated case reports of FA patient pregnancy post-HSCT have been published.,[6-8] Moreover, experimental studies suggested that FA complementation groups are required for mitotic proliferation of primordial germ cells and also that hormonal problems and sterility might be associated to specific mutations.[16,17] Unfortunately, data regarding the complementation group or additional mutations were not available for most of the described patients in our study.

The magnitude of ovarian damage in females who received HSCT is drug-specific and dose-related. Furthermore, the age at exposure has a fundamental role as younger women need higher doses of irradiation and/or alkylating agents to produce irreversible ovarian failure. It is also known that few patients may recover gonad function spontaneously even receiving conditioning with CY and/or TBI after varying intervals of time.[18,19]

The increased sensitivity to DNA-damaging agents in FA requires the use of an attenuated conditioning regimen before HSCT to avoid lethal toxicity. Nevertheless, patients with FA who undergo HSCT still present toxicity comparable to that of patients transplanted for other diseases given conventional conditioning regimens. Our data do not authorize any recommendation for conditioning Fanconi anemia patients; most regimens now use fludarabine which decreases toxicity and improves engraftment. In our own series, use of fludarabine and low-dose cyclophosphamide gives good results in terms of engraftment and long-term survival after HLA identical sibling

bone marrow transplant (Nabhian *et al.*, unpublished results, 2010). For unrelated bone marrow transplantation, most centers use the association of fludarabine, low-dose cyclophosphamide and TBI 2 Gy as described by the Minnesota group.[19-24]

Guardiola *et al.* suggested a significant correlation between survival, toxicity after transplant and extent of malformations of FA[25]. In this context, only one of our 10 patients could be considered to have an extensive malformation syndrome and none of them had developed chronic graft-*versus*-host-disease.

In most mammalian species, the production of ovarian oocytes is thought to cease after birth. However, this belief has been challenged by research indicating that female gonad have regenerative activity in juvenile and adult mice *in vivo*. Johnson *et al.* published a hypothesis postulating that fertility recovery after transplant might be the result of germ line stem cells supplied by the donor bone marrow.[26, 27] To test this hypothesis, we decided to analyze the genetic origin of the child of one of our FA patients who consented to a genetic analysis among mother, daughter and donor. These results showed clearly the genetic relationship between the transplanted patient and her daughter, excluding the possibility of germ cell transmission from the donor. This suggested that fertility recovery after BMT could only result from incomplete depletion of the ovarian follicle reserve.[28] Other studies have shown that bone marrow cells or other normally circulating cells are not involved in the formation of mature ovulated oocytes and that instead of germ line stem cells, putative thecal stem cells could be isolated from new born mouse ovaries. Therefore, the presence of female germ cells in mammals is still very controversial. More recently, Zou *et al.* identified and confirmed the presence of female germline stem cells in postnatal mammalian ovaries.[29]

Our findings also suggest that, just as for other diagnosis,[30] if pregnancy does occur in FA patients after transplant, outcome is likely to be favorable.

Obviously, numerous questions remain unanswered: is the pregnancy frequency of FA patients comparable to other transplant groups? Should our low intensity conditioning regimen be considered non-ablative for the ovaries? Is there a mechanism of fertility repair involved? And if this is so, what would be the donor bone marrow cells contribution to that? If the hypothesis of recovery of germ cells provided by donor cells is highly improbable, we cannot exclude the possibility that donor cells contribute to the repopulation of granulosa secreting factors which might repair damaged oocytes. In FA, somatic

Table 1. Cases of transplanted Fanconi's anemia and pregnancy.

Fanconi Anemia diagnosis			HSCT			Pregnancy			
Case	Age	Physical examination	Age	Conditioning Regimen	Ovarian Failure	HRT	Age	Delivery and Outcome	Baby outcome	Mother's status
1	8 y	Café au lait spots, typical face and microphtalmia	14 y	CY 20 mg/kg TBI 6 Gy + ATG	Yes	Yes	21 y	Normal	Normal	Alive
2	5 y	Low birth weight, growth retardation, café au lait spots, typical face and thumb abnormalities	6 y	CY 200 mg/kg	No	No	18 y	Normal	Normal	Alive
3	5 y	Low birth weight, typical face, thumb abnormalities and pelvic kidney	5 y	CY 20 mg/kg TAI 5 Gy	Yes	Yes	21 y	Normal - Atonic uterus and hysterectomy	Normal	Alive
4	7 y	Café au lait spots, typical face, microcephalia, congenital hip dysplasia	12 y	CY 20 mg/kg TAI 5Gy + ATG	Yes	No	21 y	Cesarean 27 w - preeclampsia	870 g	Alive
5	17 y	Normal	17 y	CY 20 mg/kg TAI 5Gy + ATG	Yes	Yes	21 y	Normal	Normal	Alive
6	9 y	Low birth weight, hypopigmentation, typical face, hyperpigmentation and congenital tracheal-esophageal fistula	14 y	CY 200 mg/kg	Yes	No	20 y 24 y	Normal Normal	Normal Normal	Died, 35 y Squamous Cell Carcinoma
7	8 y	Café au lait spots	6 y	CY 200 mg/kg	No	No	20 y 24 y	Normal Normal	Normal Normal	Alive
8	5 y	Typical face	9 y	CY 200 mg/kg TBI 5Gy + ATG	No	No	22 y 24 y	Cesarean 34 w - placental abnormality Normal 33 w	2010 g 1930 g	Alive
9	4 y	Café au lait spots, hypopigmentation and thumb abnormalities	12 y	CY 40 mg/kg + FLU 180 mg/m^2 TAI 4,5 Gy + ATG	No	No	19 y	Normal	Normal	Alive
10	10 y	Polydactyly	19 y	CY 20 mg/kg + AraC 24 g/m^2 TBI 6 Gy + ATG	No	No	23 y	Normal	Normal	Alive

HRT: hormonal replacement therapy; CY: cyclophosphamide. TBI: total body irradiation; TAI: thoraco-abdominal irradiation; ATG: anti-thymocyte globulin; FLU: fludarabine; Ara-C: cytarabine.

mosaicism is frequent; it acts as a natural gene therapy showing that genetic correction confers a selective advantage to FA stem cell, a process which might restore potential germ line stem cells.[31,32] We can speculate that oocyte mosaicism has occurred in the patients in whom spontaneous recovery of ovarian function developed after HSCT.

For now, our conclusions are that recovery of normal ovarian function and a viable pregnancy is a realistic possibility even in FA patients following allogeneic HSCT. How best to estimate ovarian reserve clinically is highly controversial. Passive assessments of ovarian reserve include measurements of serum follicle stimulating hormone (FSH), estradiol (E(2)), anti-Mullerian hormone (AMH) and inhibin B. Ultrasound determination of antral follicle count (AFC), ovarian vascularity and ovarian volume can also have a role.[11,15]

On this basis, we recommend that long-term follow up should always include: regular hormonal assessment, replacement therapy to prevent early and late unwanted effects after SCT and finally, patient information about puberty and fertility. Counseling before transplant and during follow up is very important; the patients should be followed in a gynecology unit specialized in sterility in order to propose other methods of procreation including cryopreservation of ovarian tissues before transplant or new techniques of *in vitro* fertilization.

Further analyses must include a fertility rate comparison of transplanted and non-transplanted FA females and future prospective studies might determine the influence of systemic factors related to transplantation on female fertility recovery.

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