Oocyte cryopreservation for women with GATA2 deficiency

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Abstract

Purpose To describe controlled ovarian stimulation (COS) in a population of women with GATA2 deficiency, a genetic bone marrow failure syndrome, prior to allogeneic hematopoietic stem cell transplant

Methods This is a retrospective case series of nine women with GATA2 deficiency who underwent oocyte preservation at a research institution. Main outcomes measured include baseline fertility characteristics ((antimüllerian hormone (AMH) and day 3 follicle-stimulating hormone (FSH) and estradiol (E2)) and total doses of FSH and human menopausal gonadotropins (HMG), E2 on day of trigger, and total number of metaphase II oocytes retrieved.

Results The mean age was 24 years [16–32], mean AMH was 5.2 ng/mL [0.7–10], and day 3 mean FSH was 5.1 U/L [0.7–8.1], and E2 was 31.5 pg/mL [<5–45]. The mean dose of FSH was 1774 IU [675–4035], and HMG was 1412 IU [375–2925] with a mean E2 of 2267 pg/mL [60.7–4030] on day of trigger. The mean total of metaphase II oocytes was 7.7 [0–15]. One patient was diagnosed with a deep vein thrombosis (DVT) with pulmonary embolism (PE) during COS.

Conclusion This study is the first to analyze the outcomes of COS in women with GATA2 deficiency. The response to ovarian stimulation suggests that oocyte cryopreservation should be considered prior to gonadotoxic therapy. However, due to the risk of potentially life-threatening complications, it is prudent that patients are properly counseled of the risks and are evaluated by a multi-disciplinary medical team prior to COS.

Keywords Fertility preservation · Controlled ovarian stimulation · GATA2 deficiency · Stem cell transplant

Introduction

GATA2 deficiency is a recently described genetic bone marrow failure syndrome with a constellation of manifestations, including infections with nontuberculous mycobacteria (NTM), fungi, and herpes simplex and human papillomavirus

infections (HPV) [1, 2]. Related clinical signs may include lymphedema, venous thrombosis, pulmonary alveolar proteinosis, sensorineural hearing loss, myelodysplastic syndrome (MDS), and acute myelogenous leukemia (AML). Additional malignancies include HPV-drive squamous cell carcinoma and Epstein-Barr virus-driven malignancies [1, 3]. A survival rate of only 45% at age 60 has been reported in a cohort of 57 patients [1]. Hematopoietic stem cell transplantation (HSCT) has been successfully reported to reverse the hematologic, immunologic, and clinical manifestations of the disease [4].

The genetic mutation for GATA2 deficiency was only recently discovered in 2011, although familial cases describing the disease were published as early as 1972 [5, 6]. GATA-binding protein is a zinc finger transcription factor that is paramount for hematopoiesis and lymphatic development [7, 8]. Haploinsufficient mutations on one allele in the GATA2 transcription factor underlie the syndrome [7, 8]. These mutations may be spontaneous or present in the germline and be transmitted through generations in an autosomal dominant

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fashion [3, 5, 7]. In approximately 50% of the patients, the mutations arise de novo and family members will not harbor the mutation. Since the recent diagnosis of GATA2 deficiency, the clinical manifestations and morbidity of the disease are beginning to be elucidated. In a published cohort of GATA2 deficiency patients, presentation of the disease occurred as early as 5 months of age and as late as 78 years old although the median age was 20 years [1]. There is variable expressivity of the disease with some individuals with the mutation remaining asymptomatic throughout their lifetime, whereas, other family members require HSCT as teenagers. In a literature review compiling 378 cases, 75% of GATA2 patients developed myeloid neoplasia at a median age of 20 years [9].

The most common initial presentation of GATA2 deficiency consists of treatment-resistant cutaneous warts driven by HPV. These patients routinely present first to a dermatologist or gynecologist [1]. Prompt diagnosis facilitates timely treatment, prior to the onset of life-threatening disease, and HSCT [1, 4]. The disease-free survival rate following HSCT in 22 patients with GATA2 deficiency treated at the National Institutes of Health (NIH) using a busulfan-based regimen was 85% (D. Hickstein, submitted). In a pediatric cohort of 34 GATA2 patients, the 5-year survival rate was 66% after HSCT [10].

The majority of GATA2 patients undergoing HSCT are young adults, and the high-dose conditioning regimens used for HSCT are anticipated to result in infertility. The age at transplantation, exposure to alkylating agents, and the use of total body irradiation in haploidentical-related donor regimens all contribute to the risk of gonadal failure in both men and women [11, 12]. Thus, the cryopreservation of oocytes or sperm must be discussed prior to HSCT. Previous studies have shown that for women undergoing HSCT for hematological and non-hematological malignancies, 65–84% will be diagnosed with premature ovarian failure [12]. This is understandably a source of great anxiety for patients. Thus, the importance of fertility preservation counseling is critical. The role of fertility preservation in a newly identified rare disease complicates fertility preservation in this population, as the effect of the disease on the reproductive system is not completely understood. It is known that the GATA2 gene is expressed throughout the body and is involved in uterine progesterone signaling, pituitary function, and regulation of trophoblast gene expression [13–15]. Subsequently, patients with GATA2 deficiency may be inherently at risk for poor reproductive outcomes. However, there is insufficient evidence to determine its influence on reproductive outcomes in this population. There are no published studies regarding the fertility of males with GATA2 deficiency. One study reported obstetric complications in women with GATA2 deficiency. A cohort of 14 females self-reported 43 pregnancies, and information on live births and miscarriages was collected.

The miscarriage rate was noted to be 33%. However, of the 14 miscarriages reported, eight of the miscarriages occurred in a single patient [1]. At this time, no conclusion of obstetric outcomes in patients with GATA2 deficiency can be drawn.

As knowledge of GATA2 deficiency continues to grow, it is essential that the reproductive health of these patients be studied in parallel with their hematologic disease. The NIH follows a large number of patients with GATA2 deficiency, providing the opportunity to evaluate patients undergoing COS. The purpose of this case series is to present the baseline fertility characteristics of GATA2 deficiency and evaluate the efficacy and safety of ovarian stimulation for the purpose of oocyte cryopreservation.

Material and methods

This is a retrospective case series of patients who received care at the NIH in Bethesda, Maryland, between March 2015 and March 2017. Patients were recruited through Institutional Review Board-approved natural history protocols for the study of NTM infection, primary immune deficiency, or inherited bone marrow failure syndromes. Patients subsequently were found to harbor GATA2 mutations. Patients who were determined to have a life expectancy of greater than 3 months, but less than 2 years of life, and had a history of three episodes of life-threatening infections were appropriately counseled and, under informed consent, enrolled in NIH Protocol 13C0132: “Allogeneic HSCT for Patients with GATA2 Deficiency or the MonoMac Syndrome.” Female patients were then referred to the Reproductive Endocrinology department for fertility counseling and were enrolled in protocol 14-CH-0177 “Fertility Preservation in Women Who Will Have Gonadotoxic Therapy or Hematopoietic Stem Cell Transplantation, and in Women With Sickle Cell Disease.” Postmenarchal females were offered fertility preservation. Patients who were less than 18 years old also received an ethics consultation to further enhance their understanding of the impact of the HSCT and potential use of cryopreserved oocytes in the future. A multidisciplinary team composed of specialists in infectious disease, hematology, transplant medicine, genetics, and reproductive endocrinology and infertility coordinated the care of each individual patient. Baseline characteristics were collected on nine patients who underwent fertility preservation using controlled ovarian hyperstimulation and oocyte cryopreservation following guidelines set forth by the OncoFertility Consortium [16]. The mean age was 24 years (range 16–32), mean Antral Follicle Count (AFC) was 26.7 (range 10–43), and mean anti-müllerian hormone (AMH) was 5.16 ng/mL (range 0.7–10) (Table 1). All of the patients were nulliparous, and no patient had attempted to become pregnant in the past.

Table 1 Baseline characteristics

	Case 1*	Case 2*	Case 3	Case 4	Case 5**	Case 6**	Case 7	Case 8	Case 9	Case 10	Case 11***	Case 12***
Age	29	29	29	16	23	23	17	24	18	32	28	28
AFC	17	13	13	36	31	39	35	37	10	13	33	43
AMH	1.3	1.3	1.4	2.05	6	6	5.9	8.4	N/A	0.7	10	10
FSH	2	0.7	1.3	3.5	8	7.2	8.1	7	7.2	7.4	2.1	6.2
LH	2.9	0.2	0.7	1.26	8.4	15.8	5.5	9.4	4.2	6.5	3.6	5.5
E2	<5	<5	33.6	22	41	15.1	33	38	27.6	39.2	30	45

*Denotes individuals who underwent multiple cycles. *AFC* antral follicle count, *AMH* antimüllerian hormone (ng/ml), *FSH* follicle-stimulating hormone on cycle day 3 (IU/l), *LH* luteinizing hormone on cycle day 3 (IU/L), *E2* estradiol cycle day 3 (pg/ml)

Ovarian stimulation

Prior to the start of ovarian hyperstimulation, patients were prescribed an oral contraceptive pill containing 35 mcg or less of ethinyl estradiol. Only one patient did not receive an OCP, which was due to timing constraints. Due to the risk of VTE, all patients were evaluated by a hematologist at the NIH prior to initiation of therapy and were started on venous thromboembolism (VTE) prophylaxis with either heparin or enoxaparin if they were considered high risk for VTE. Due to the high risk of infection in this population, patients were commonly prescribed prophylaxis for pneumonia at the time of diagnosis of the disease. Thus, it was common for patients to start ovarian hyperstimulation while receiving medications such as augmentin or azithromycin. One patient with a history of aspergillus continued to receive oral azole therapy for prophylaxis. That same patient also received ethambutol, moxifloxacin, and azithromycin for a history of pulmonary MAC. HSV prophylaxis was continued in all patients with a history of HSV. No patients required steroids prior to or during ovarian hyperstimulation and oocyte retrieval. All patients were placed on antagonist protocols to enable determination of human chorionic gonadotropin (HCG) vs leuprolide acetate trigger prior to oocyte retrieval. The dosage of the gonadotropins (Gonal-F, EMD-Serono; Follistim, Merck and/or Menopur, Ferring) was determined based on the patient's age, assessment of her respective ovarian reserve, and stimulation protocol starting on cycle day 3. Patients were followed either daily or every other day, and medication doses were adjusted based on E2 levels and follicle sizes on ultrasound. Ganirelix acetate 250 mcg was initiated on cycle day 6 or with lead follicle measurement of 14 mm. Either HCG 10,000 international units or leuprolide acetate 4 mg trigger was administered when at least two follicles were greater than 18 mm in size. Oocyte retrieval was scheduled 36 h following trigger administration. Doxycycline or azithromycin was administered prior to procedure for prophylaxis. Oocyte cryopreservation via vitrification of mature and immature oocytes was performed the day of retrieval.

Results

The mean dose of FSH was 1774 IU plus 1412 IU of HMG with a mean total of 11 stimulation days. Patients had a mean estradiol of 2267 pg/mL on day of trigger (Table 2). Leuprolide acetate trigger was administered in four cases that were deemed to be at risk for ovarian hyperstimulation syndrome (Table 3). The mean number of total oocytes retrieved was 12.3 and mean MII oocytes of 6.7 (Table 2).

Two patients (cases 1–2 and cases 5–6) underwent two cycles of ovarian stimulation and egg retrieval. One patient (cases 11–12) underwent two rounds of ovarian stimulation

Table 2 Mean and range of baseline characteristics and results of fertility preservation cycle

	Mean	Range
Age, y	24.7	16–32
AFC	26.7	10–43
AMH	5.2	0.7–10
Baseline FSH	5.1	0.7–8.1
Baseline E2	31.5	<5–45
Baseline P	1.72	0.2–11.4
Day 6 E2	555.8	111.5–1214
Day 6 P	0.675	0.3–1.2
Total FSH	1774	675–4035
Total HMG	1412	375–2925
Total stimulation days	11	7–14
E2 on day of trigger	2267	60.7–4030
P on day of trigger (ng/mL)	1.58	0.3–3.1
Follicle number on day of trigger > 10 mm	12.5	6–21
Total oocytes	12.3	4–28
Total mature oocytes (MII)	6.7	0–15

AFC antral follicle count, *AMH* antimüllerian hormone (ng/ml), *FSH* follicle-stimulating hormone (IU/l), *LH* luteinizing hormone (IU/L), *E2* estradiol (pg/mL), *P* progesterone (ng/mL), *HMG* human menopausal gonadotropins (IU/l)

Table 3 Results of ovarian stimulation per individual case

	Case 1*	Case 2*	Case 3	Case 4	Case 5**	Case 6**	Case 7	Case 8	Case 9	Case 10	Case 11***	Case 12***
Total FSH dose	2175	4035	1650	1958.2	949.8	1274.7	1899.9	675	2400	2325	900	1050
Total HMG dose	1500	2700	2925	1500	936	1800	1387.5	675	1650	375	975	525
Total Stimulation days	12	14	10	11	10	13	12	9	12	10	12	7
E2 on day of trigger	3973	2722	673	1726	2064	4030	2156	3522	3190	1241	60.7	1855
P on day of trigger	3.1	0.8	1.1	0.9	0.7	1.1	1.7	1.5	0.3	0.4	0.8	1.5
Trigger	Hcg trigger 10,000 IU	Hcg trigger 10,000 IU	Lupron 4 mg	Hcg trigger 10,000 IU	Hcg trigger 10,000 IU	Lupron 4 mg	Hcg trigger 10,000 IU	Lupron 4 mg	Lupron 4 mg	Hcg trigger 10,000 IU	Hcg trigger 10,000 IU	Hcg trigger 10,000 IU
Total follicles	11	8	8	9	14	20	15	19	21	10	6	9
Total oocytes retrieved	13	15	4	10	5	28	12	13	22	7	N/a	6
Total mature oocytes (MII)	10	8	3	10	5	15	6	9	8	0	N/a	0

*Denotes individuals who underwent multiple cycles. FSH follicle stimulating hormone (IU/l), HMG human menopausal gonadotropins (IU/l), E2 estradiol (pg/mL), P progesterone (ng/mL)

and one egg retrieval. In case 11, the cycle was canceled due to a sudden drop of E2 during stimulation. Patient began ovarian stimulation with a starting dose of 75 IU of FSH and 75 IU of HMG. On stimulation day 4, E2 was 353 pg/mL and progesterone (P) was 1 ng/mL. HMG was stopped on stimulation day 5 due to elevated E2 value and FSH 75 IU was continued. On stimulation day 6, E2 was 895 pg/mL and P was 0.9 ng/mL with a lead follicle of 14 mm. Ganirelex was started the next day. On stimulation day 8, E2 was 847 pg/mL and P was 1.0 ng/mL. There were ten follicles measuring less than 10 mm plus 12 follicles greater or equal to 10 mm, the largest of which was 19 mm. Unexpectedly, E2 dropped to 60 pg/mL and P was 0.8 ng/mL on stimulation day 11. The blood work was repeated, and results were consistent. The decision was made to cancel the cycle. The patient's second cycle, case 12, resulted in the recovery of six oocytes, none of which were mature. There was one case of venous thrombosis and subsequent pulmonary embolism during ovarian stimulation. The patient had not been placed on prophylactic anticoagulation during ovarian stimulation as she had been categorized as low risk by the hematologists. She had no personal or family history of VTE, was mobile, and did not have a history of lymphedema or malignancy. She was subsequently anticoagulated and still proceeded with oocyte retrieval, after the primary team assessed her to be stable and asked us to proceed, without further complications.

Discussion

These results indicate that oocyte cryopreservation in patients with GATA2 deficiency is feasible. None of the nine patients have yet to attempt fertilization with the cryopreserved oocytes at the time of this publication. Thus, we are not yet able to report pregnancy rates following fertility preservation in this population. None of the patients in our cohort had either attempted to become pregnant or had conceived in the past. HSCT may afford them to opportunity to consider building a family once their health improves. While HSCT for GATA2 deficiency patients is not yet a global standard of care, it is standard of care to offer all women undergoing gonadotoxic therapy consultation with a fertility specialist to discuss options available for fertility preservation [17]. It is expected that some patients with severe immunodeficiency related GATA2 mutations may not be candidates for oocyte preservation due to extensive co-morbidities. However, it is important to discuss future fertility to all patients undergoing gonadotoxic therapy, as one study found that patients diagnosed with breast cancer ranked future infertility as a major concern and 29% reported that infertility concerns had influenced their treatment decisions [18]. In our experience, the GATA2 deficiency patients and other young females with hematologic disorders frequently delay life-saving HSCT therapies due to concerns

of the gonadotoxicity of the treatments. Patients who are subject to rigorous treatment regimens for life-threatening diseases find it easier to cope with the burden of treatment after they have undergone fertility preservation [19].

We encountered one significant life-threatening complication during COS. Of the nine women, one patient was diagnosed with a DVT and PE. Although she was not identified as a high risk for VTE, it has been reported from a case series of 57 patients with GATA2 deficiency that the incidence of VTE was 25% [1]. While the risk of VTE during COS has been reported to be greatest in patients who are diagnosed with ovarian hyperstimulation syndrome (OHSS), IVF itself has not been associated with an increase in VTE [20]. The literature is scarce in terms of reporting the incidence of VTE in cancer patients undergoing fertility preservation, and there is insufficient evidence to suggest that this COS in the absence of OHSS and pregnancy poses an increased risk of VTE in cancer patients [21, 22]. Due to our unique patient population, it is necessary to extrapolate outcomes from research in other disease populations. It is the recommendation of our multidisciplinary team that patients with GATA2 deficiency be administered prophylactic anticoagulation if there is a personal or family history of VTE, significant lymphedema, decreased mobility, malignancy, or other risk factors for VTE such as a diagnosis of an acquired or inherited thrombophilia. Avoidance of OHSS in our patient population is vital to decrease their risk of VTE. In addition, incorporation of letrozole in our stimulation protocol may be of benefit to reduce the exposure to high E2 [23]. While letrozole is almost universally used to prevent progression of hormone-sensitive cancer during fertility preservation, it may also serve as a protective measure against VTE. There is evidence that COS may induce a hypercoagulable state as one studied demonstrated a rise in fibrinogen and reduction in antithrombin III in 12 women undergoing ovarian stimulation for IVF [24]. Elevated E2 levels may contribute to the hematologic changes noted during stimulation but correlation has not been studied. Future studies are indicated to determine if letrozole may be beneficial in our patient population and other at risk populations to decrease the risk of VTE.

One of the greatest challenges in offering fertility preservation to patients with rare diseases is the inability to a priori predict their responses to ovarian stimulation. It is reassuring that the baseline fertility testing in this population appears to be similar to that of the general population. However, the impact of GATA2 deficiency and subsequent illness may pose substantial risk for successful ovarian stimulation. For example, in a meta-analysis from 227 untreated cancer patients and 1258 controls from seven studies, the total oocytes and mature oocytes retrieved differed between the two groups when controlled for age. The mean number of oocytes retrieved was significantly lower in the study group than the control group (11.7 versus 13.5, $P = 0.002$), and the mean number of mature

oocytes was also significantly lower in the study group (9.0 versus 10.8, $P = 0.002$) [25]. While direct comparison to our population cannot be made, it is important to note that the mean total number of mature oocytes collected was less than expected, with a mean of 12.3 total oocytes retrieved with 6.7 mature oocytes. Both immature and mature oocytes were cryopreserved. The preservation of immature oocytes is considered investigational currently but was performed due to the low yield of mature oocytes in some cycles and the limited number of cycles the patients could undergo due to impending HSCT. Many of our patients will be limited further by a low number of embryos available if they elect to undergo preimplantation genetic diagnosis (PGD) to detect the presence of these autosomal dominant GATA2 mutations. Thus, the decision to cryopreserve immature oocytes was made. In vitro maturation (IVM), although investigational, is expected to become a reliable technique in the near future which will benefit these patients. In one study, 33% of immature oocytes survived cryopreservation and underwent successful IVM [26]. While the cryopreservation of mature oocytes remains the primary goal, the potential of immature eggs to result in live birth does exist. IVM has already resulted in the births of healthy children, and it is expected that this process will continue to evolve [27, 28].

There are currently no reports of patients with GATA2 deficiency undergoing IVF with PGD. However, published reports utilizing PGD in other rare diseases do exist and suggest that PGD in our patient population is feasible [29–32]. Whole-exome sequencing is increasingly being utilized to identify causative genes in patients with a range of phenotypes suggesting genetic causes [33]. All of our patients underwent whole-exome sequencing as part of the protocol. As of 2017, over 100 germline mutations in the GATA2 gene have been reported [9]. However, not all patients diagnosed with GATA2 deficiency will have a known pathologic mutation and thus, PGD is not possible to prevent the transmission of the germline mutation for these patients. While it is assumed that patients undergoing PGD may require a greater cohort of embryos due to the intention to choose only those that are negative for the mutation, there are no studies to date which predict the number needed to achieve live birth in this cohort. For patients undergoing elective and medically indicated fertility preservation, Doyle et al. found that the cryopreservation of 15–20 mature oocytes resulted in a 70–80% chance for at least one live birth in patients who are less than 37 years old [34]. This number does aid in counseling patients in the general population. However, patients undergoing PGD, especially for a dominant mutation, will likely have less non-affected embryos available for transfer. In one study of 44 couples affected by a single-gene disorder who underwent 95 IVF cycles with PGD, the live birth rate was 22% per cycle initiated and 29% per embryo transferred. When including outcomes of couples undergoing IVF/PGD for chromosome

rearrangements, single-gene disorders, or X-linked conditions, 97% of live births occurred during the first two cycles. There was a significant difference in live birth rates in the first two cycles when more than nine mature oocytes were collected ($P=0.018$) and when there were at least two unaffected embryos available for transfer ($P<0.001$) [31]. The ESHRE PGD consortium reported similar results, with a live birth rate of 31% per embryo transfer for patients undergoing PGD for single-gene disorders [35]. When comparing their results to the national registry, the ESHRE PGD Consortium does report a live birth rate of 25% per oocyte, which is quite lower than the 41.2% live birth rate per oocyte reported by the 2015 SART Preliminary Clinical Summary Report [36]. The ESHRE PGD consortium reported on average, per cycle, a total of 13 retrieved oocytes. 10.7 oocytes were mature, 8.1 oocytes were fertilized, and 6.5 embryos were biopsied. The ability to reach a diagnosis for the gene defect was achieved for 5.8 embryos. Patients, on average, had 1.2 embryos transferred and 0.7 embryos cryopreserved [35]. Prior studies suggest that for patients undergoing IVF/PGD for single-gene disorders, a greater number of oocytes are needed to achieve similar reproductive outcomes of patients undergoing IVF without PGD [31, 37].

The transcriptional factor GATA2 is implicated for maintaining normal reproductive function. It is essential for progesterin activation in a variety of cells, such as endometrial tissue and mammary cells [13, 38]. In the pituitary, GATA2 has been identified in mouse gonadotropes and has been shown to increase luteinizing hormone β -subunit gene promoter activity [39]. Our cohort of patients with GATA2 deficiency undergoing ovarian stimulation exhibited P levels on day of trigger (mean 1.58 ng/mL) similar to those of the general population undergoing embryo cryopreservation [40]. While our population was not able to proceed with a fresh embryo transfer, our patients may be at risk of premature P elevation. While there is no defined cutoff for premature P elevation, P levels of 1.0–1.88 ng/mL are often used [41–44]. In oocyte-donor programs, premature P elevation, when defined as P values greater than 1.2 ng/mL, did not correlate with ongoing pregnancy rate [43]. We infer that GATA2 deficiency patients are not at elevated risk of implantation failure after a frozen embryo cycle. However, it will be important to evaluate embryo quality, endometrial receptivity, and rates of implantation, pregnancy, and live birth in the future. GATA2 dependent transcription factors are responsible for P signaling in early pregnancy; in the mouse model, absence of GATA2 results in failure of embryo implantation, endometrial decidualization, and uninhibited estrogen signaling [13]. The effect of HSCT on GATA2 reproductive system functions is unknown but will be crucial to determine.

Fertility preservation in patients with rare diseases by definition presents unique challenges. Rare diseases are often difficult to study due to the small number of the population

affected and the lack of resources available. As GATA2 deficiency is a newly diagnosed disease, our experience with oocyte preservation in nine patients is unique and reporting the results may be of value to other institutions where a cohort of patients with GATA2 deficiency is unlikely to be encountered. Future investigation of fertility preservation in GATA2 patients is needed to adequately counsel patients on expectations, especially regarding live birth rates after HSCT. In addition, patients with GATA2 deficiency may be at greater risk of medical complications, such as the risk of VTE. A multi-disciplinary team is necessary to ensure that complex risks are properly managed. This study is the first to report the outcomes of oocyte cryopreservation in patients with GATA2 deficiency. The procedure was generally well tolerated and safe, with only reported complications encountered, despite multiple medical comorbidities. This procedure should be strongly considered in the care of fertile women diagnosed with GATA2 deficiency.

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