Objective: To describe fertility characteristics, outcomes of oocyte cryopreservation cycles, and safety of ovarian stimulation in patients with GATA binding protein 2 (GATA2) deficiency, dedicator of cytokinesis 8 (DOCK8) deficiency, and sickle cell disease (SCD) preparing for hematopoetic stem cell transplantation (HSCT).

Design: Retrospective case series.

Setting: The National Institutes of Health.

Patient(s): Female patients with GATA2 deficiency, DOCK8 deficiency, and SCD aged between 13 and 38 years.

Intervention(s): None.

Main Outcome Measure(s): Demographic and ovarian reserve parameters, stimulation outcomes, and adverse event occurrences were collected through chart review. Descriptive statistics were used to identify trends within disease subcategories.

Result(s): Twenty-one women with GATA2 deficiency, DOCK8 deficiency, and SCD underwent fertility preservation prior to HSCT. Patients with DOCK8 deficiency had the lowest mean age (16.5 years old) and antimüllerian hormone (0.85 ng/mL). Patients with GATA2 deficiency had the highest antral follicle count and antimüllerian hormone (25.77 and 5.07 ng/mL, respectively). Baseline follicle-stimulating hormone, luteinizing hormone, and estradiol were comparable between the cohorts. The duration of stimulation was similar (10.43 to 11.25 days) across all groups. Comparable peak estradiol levels were achieved across the cohorts. Patients with SCD had the highest mature (MII) oocyte yield (10.71). Three patients experienced complications related to stimulation: pain crisis in a patient with SCD, pulmonary embolism, and zero oocytes cryopreserved in a patient with GATA2 deficiency.

Conclusion(s): This study offers insight into controlled ovarian stimulation in patients with these conditions prior to HSCT. Oocyte cryopreservation can be performed successfully, although adverse events must be considered. Following the outcomes of gamete use in this cohort will serve to further our knowledge of the true reproductive potential of this population. (Fertil Steril Rep® 2020;1:287–93. © 2020 by American Society for Reproductive Medicine.)

Key Words: Fertility preservation, hematopoetic stem cell transplantation, sickle cell disease, GATA2 deficiency, DOCK8 deficiency

Discuss: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/posts/xfre-d-20-00132
Improved patient survivorship after hematopoietic stem cell transplantation (HSCT) has resulted in a paradigm shift toward multidisciplinary treatment planning and an emphasis on post-treatment life goals. Men and women of childbearing age with medical conditions requiring gonadotoxic therapies are now given the option to undergo fertility preservation before treatment. Ovarian failure has been reported in more than 90% of adults and 65%–84% of children after HSCT, bringing fertility preservation to the forefront of comprehensive treatment planning in these patients (1).

Advances and research efforts in female fertility preservation techniques are expanding the potential options available to women to safeguard their future fertility. Cryopreservation of oocytes or embryos and ovarian tissue cryopreservation are currently the only therapeutic options for fertility preservation endorsed by the American Society for Reproductive Medicine (2, 3). Other methods of fertility preservation including in vitro maturation of immature oocytes are currently under investigation (4). Ovarian transposition and the use of gonadotropin–releasing hormone agonists are other techniques less commonly used (4–6). Oocyte cryopreservation, which had its experimental label lifted by the American Society for Reproductive Medicine in 2012, protects patients’ reproductive autonomy and provides promising rates of live clinical births (7).

Ovarian function and the response to controlled ovarian stimulation (COS) for oocyte cryopreservation may be affected by underlying disease processes. A number of single-gene disorders have been linked with female infertility due to pathogenesis of the disease (8). Given that many of these mutations are linked with an increased rate of follicular depletion, it is unclear whether these patients are more susceptible to ovarian failure following HSCT or whether their response to ovarian stimulation greatly differs from the general population of women undergoing oocyte cryopreservation (9). Understanding these interactions will improve our ability to set appropriate expectations and accurately counsel patients before initiating treatment.

In 2014, the department of Reproductive Endocrinology and Infertility at the National Institutes of Health (NIH) established a protocol with the sole purpose of providing oocyte cryopreservation for women with medical conditions necessitating gonadotoxic therapies under other NIH protocols. Patients were often afflicted by rare conditions such as GATA binding protein 2 (GATA2) deficiency or dedicator of cytokinesis 8 (DOCK8) deficiency. Inherited or sporadically acquired deficiency of the transcription factor GATA2 is characterized by bone marrow failure affecting multiple organ systems. These patients are faced with various degrees of myelodysplasias, myeloid leukemias, viral and bacterial infections, and lymphedema (10). The most common gynecologic finding in this unique population is cutaneous human papilloma virus (HPV) infection (11). Patients with an autosomal recessive deletion of the DOCK8 gene exhibit a form of hyperimmunoglobulin E syndrome that manifests as a primary immunodeficiency (12). Like patients with GATA2 deficiency, these patients often present with extensive HPV infections among other viral infections (12). Although there has been no definitive data linking these single-gene mutations to adverse reproductive outcomes, their interplay with progesterone (P) signaling suggests there may be an underlying impact on fertility (14–16). Additionally, the program also has attracted women with sickle cell disease (SCD) and other rare disorders facing gonadotoxic treatments.

Dedicator of cytokinesis 8 deficiency, GATA2 deficiency, and SCD can all be treated with HSCT, which often results in infertility (12, 13, 17–19). The aim of this study was to describe the baseline fertility characteristics and outcomes of COS in patients with GATA2 deficiency, DOCK8 deficiency, and SCD prior to HSCT. Our secondary goal was to report on the safety of COS and rate of adverse events in an effort to continue the development of our fertility preservation program and further the knowledge of fertility preservation in these disease populations.

**MATERIALS AND METHODS**

This was a retrospective case series of female patients with GATA2 deficiency, DOCK8 deficiency, and SCD undergoing fertility preservation prior to HSCT with the Department of Reproductive Endocrinology and Infertility at NIH between September 2014 and December 2019. Patients were first recruited to the NIH through Institutional Review Board–approved protocols specific to their institute. All reproductive-age females (postmenarchal and premenopausal) participating in NIH research protocols requiring medical treatment with gonadotoxic therapy were eligible for screening consultation. Screening consultation included a medical history, physical examination, serum screening with complete blood count and infectious disease panel (human immunodeficiency virus, hepatitis B, hepatitis C, human T-lymocyte virus, cytomegalovirus, syphilis, gonorrhea, and chlamydia), and baseline hormonal evaluation on day 3 of the menstrual cycle (antimüllerian hormone [AMH], follicle-stimulating hormone [FSH], luteinizing hormone, and estradiol [E2] levels). Abdominal or transvaginal ultrasound was performed to measure antral follicle count (AFC) in most cases. Given the association of some of these conditions with HPV-related disease, it was confirmed that all patients had up-to-date cervical cancer screening. Additionally, patients younger than 16 years of age received a bioethics consultation.

Inclusion criteria for participation included postmenarchal females with GATA2 deficiency, DOCK8 deficiency, and SCD anticipating HSCT with baseline FSH ≤ 13 IU/L or AMH ≥ 0.50 ng/mL and the absence of any medical contraindications to ovarian stimulation or oocyte retrieval. Eligible patients were then either enrolled in protocol number 14-CH-0177 “Fertility preservation in females who will be undergoing gonadotoxic therapy hematopoietic stem cell transplantation, and in females with sickle cell disease” or had a formal referral placed to the fertility preservation consultation service. The care plan for each patient was made with a multidisciplinary approach involving the
patient’s primary treatment team (infectious disease, hematology/oncology, transplantation medicine, and genetics) and the reproductive endocrinology and infertility team.

Ovarian stimulation was conducted at the NIH and protocols were tailored to the patients’ unique clinical situations. Due to transplantation-related time constraints, the majority of patients had initiation of ovarian stimulation in conjunction with spontaneous menses or had random cycle starts. Occasionally, patients without any absolute contraindications to hormonal contraceptives initiated gonadal down-regulation with oral contraceptive pills for 2–6 weeks prior to stimulation. Those deemed at high risk of thromboembolism after evaluation by hematology were started on thromboprophylaxis with enoxaparin. Many patients were prescribed antimicrobial prophylaxis for pneumonia given their transplantation-related time constraints. Due to transplantation-related time constraints, the majority of patients met inclusion for our review: 11 had GATA2 deficiency, 4 had DOCK8 deficiency, and 6 had SCD. Four women (3 with GATA2 deficiency and 1 with SCD) underwent two cycles of stimulation for oocyte cryopreservation for a total of 25 cycles. Baseline characteristics by medical condition are listed in Table 1. The mean age of patients was 27.42 years in patients with SCD, 23.93 years in patients with GATA2 deficiency, and 16.50 years in patients with DOCK8 deficiency (the youngest cohort of the three groups). The median parity for all three groups was zero. Patients with DOCK8 deficiency had the highest mean AFC and AMH levels (26.9 years in patients with SCD, 23.9 years in patients with GATA2 deficiency, and 16.50 years in patients with DOCK8 deficiency). A higher dose of mean gonadotropins (recombinant FSH (2,387.50 IU) was used in patients with DOCK8 deficiency and/or human menopausal gonadotropin (HMG; Menopur, Ferring Pharmaceuticals)). Gonadotropin dosages were determined on a case-by-case basis by incorporating various patient factors (age, ovarian reserve, and stimulation protocol) to maximize ovarian follicle development while minimizing the risk of ovarian hyperstimulation. Patients were monitored with serial ultrasound as well as serum E2 and P measurements to allow for dose adjustments as needed. Ganirelix acetate (Merck) (250 µg/d) was initiated on day 6 of stimulation or when the lead follicle reached 14 mm in size. Based on the patient’s baseline laboratory results and stimulation outcome, they were triggered with either 4 mg leuprolide acetate or 10,000 IU human chorionic gonadotropin (hCG) when at least two follicles reached 18 mm in diameter. Oocyte retrieval was performed via a transvaginal approach at NIH or Walter Reed National Military Medical Center 35 hours after the administration of the ovulation trigger. Oocyte cryopreservation via vitrification of mature (MI) oocytes was performed on the day of retrieval. Patients were administered prophylactic doxycycline or azithromycin postretrieval. When applicable, antiocoagulation was restarted generally on postoperative day 1 and was continued for up to 4 weeks; however, any variations were determined on a case-by-case basis with the assistance of the hematology department.

All information was obtained via chart review. Outcomes examined included stimulation protocols, procedural outcomes, and complications. Descriptive statistics using Microsoft Excel were used to evaluate for trends.

RESULTS
A total of 21 patients met inclusion for our review: 11 had GATA2 deficiency, 4 had DOCK8 deficiency, and 6 had SCD. Four women (3 with GATA2 deficiency and 1 with SCD) underwent two cycles of stimulation for oocyte cryopreservation for a total of 25 cycles. Baseline characteristics by medical condition are listed in Table 1. The mean age of patients was 27.42 years in patients with SCD, 23.93 years in patients with GATA2 deficiency, and 16.50 years in patients with DOCK8 deficiency (the youngest cohort of the three groups). The median parity for all three groups was zero. Patients with DOCK8 deficiency had a baseline AMH level of 0.85 ng/mL and mean AFC level of 8.10. Patients with GATA2 deficiency had higher mean AFC and AMH levels (25.8 and 5.1 ng/mL, respectively) than the other two groups. The remaining baseline laboratory values (FSH, luteinizing hormone, and E2) were comparable between the three groups.

Outcomes of ovarian stimulation by condition are reported in Table 2. All patients underwent ovarian stimulation with an antagonist protocol as described. On average, the patients with DOCK8 deficiency had the longest duration of stimulation (11 days on average), although this was not markedly different from the other groups. A higher dose of mean recombinant FSH (2,387.50 IU) was used in patients with DOCK8 deficiency. Patients with DOCK8 deficiency had the largest mean peak E2 of 2,993.00 pg/mL; however, the other two cohorts had comparable levels. Across all three conditions, there were no failed triggers and zero cases of ovarian hyperstimulation syndrome (OHSS).

Patients with GATA2 deficiency had the lowest mean total oocytes retrieved (13.5) with a mean of 8.2 MII oocytes. In contrast, patients with SCD had the highest yield with a mean of 18.3 total oocytes and 10.7 MII oocytes. One patient in our GATA2 cohort did not have any oocytes cryopreserved, despite two attempts at ovarian stimulation. In her first cycle, after down-regulation with oral contraceptive pills, she was started on 75 IU of rFSH and 75 IU of HMG daily. She reached an E2 of 895 pg/mL on day 6 of stimulation with lead follicles of 14 mm when the antagonist was started. However, on day 6 of stimulation, she was continued for up to 4 weeks; however, any variations were determined on a case-by-case basis with the assistance of the hematology department.
| Patient age (y) | Diagnosis  | Total days of stimulation | Total rFSH   | Total HMG    | Peak E2    | Total oocytes | Total mature oocytes |
|----------------|------------|----------------------------|--------------|--------------|------------|---------------|---------------------|
| 20             | SCD        | 10.43 (9–12)               | 1,617.86 (975–2,325) | 1,564.29 (1,125–2,400) | 2,889.14 (1141–5,727) | 18.29 (7–30) | 10.71 (5–20) |
| 24             | SCD        | 10                        | 975          | 1,125        | 1,909      | 23            | 6                  |
| 20             | SCD        | 10                        | 2,325        | 1,725        | 5,727      | 24            | 10                 |
| 20             | SCD*       | 12                        | 1,500        | 2,100        | 2,799      | 30            | 20                 |
| 37             | SCD        | 9                         | 1,650        | 1,200        | 1,141      | 7             | 5                  |
| 32             | SCD        | 9                         | 1,200        | 2,400        | 1,255      | 18            | 13                 |
| 29             | GATA2      | 10.79 (7–14)               | 1,650.56 (675–3,675) | 1,439.21 (450–3,075) | 2,809.21 (799–4,474) | 13.46 (4–28) | 8.23 (0–18) |
| 16             | GATA2      | 11                        | 3,675        | 3,075        | 2,886      | 15            | 8                  |
| 23             | GATA2      | 10                        | 1,958        | 1,500        | 1,726      | 12            | 10                 |
| 29             | GATA2*     | 10                        | 950          | 936          | 3,239      | 5             | 5                  |
| 24             | GATA2      | 12                        | 1,275        | 1,800        | 4,210      | 28            | 15                 |
| 29             | GATA2      | 11                        | 1,650        | 2,825        | 799        | 4             | 3                  |
| 17             | GATA2      | 12                        | 1,900        | 1,388        | 2,366      | 12            | 6                  |
| 24             | GATA2      | 10                        | 675          | 675          | 4,474      | 13            | 9                  |
| 32             | GATA2      | 10                        | 1,200        | 450          | 1,345      | 8             | 1                  |
| 28             | GATA2*     | 12                        | 825          | 825          | 895        | Not retrieved | Not retrieved |
| 18             | GATA2      | 12                        | 1,050        | 525          | 3,117      | 6             | 0                  |
| 22             | GATA2      | 9                         | 2,400        | 1,650        | 3,967      | 22            | 8                  |
| 17             | GATA2      | 8                         | 1,050        | 1,800        | 4,003      | 16            | 14                 |
| 13             | DOCK8      | 11                        | 1,350        | 1,575        | 3,410      | 19            | 9                  |
| 13             | DOCK8      | 10                        | 2,025        | 2,465        | 14         | 13            | 8                  |
| 24             | DOCK8      | 12                        | 2,925        | 2,175        | 1,909      | 12            | 10                 |
| 16             | DOCK8      | 12                        | 1,575        | 1,275        | 4,117      | 10            | 9                  |
| 13             | DOCK8      | 11                        | 3,700        | 1,575        | 3,410      | 19            | 9                  |
| 13             | DOCK8      | 10                        | 1,350        | 2,025        | 2,465      | 14            | 6                  |

Note: Aggregate results for each disease subgroup reported as mean (range) unless otherwise specified. DOCK8 = DOCK8 deficiency; E2 = estradiol (pg/mL); GATA2 = GATA2 deficiency; HMG = human menopausal gonadotropin (IU); rFSH = recombinant follicle-stimulating hormone (IU); SCD = sickle cell disease.

* Patient underwent 2 cycles.

Aslerlind. Oocyte freezing before stem cell transplantation. Fertil Steril Rep 2020.
We described the outcomes of oocyte cryopreservation cycles in women diagnosed with DOCK8 deficiency, GATA2 deficiency, and SCD prior to HSCT. Conditioning regimens for HSCT involve high-dose chemoradiotherapy, which leads to ovarian destruction. Biopsy specimens from patients exposed to these agents show ovarian fibrosis and impairment of follicular maturation. Spontaneous conception following HSCT has been reported, but close monitoring is advised due to an increased frequency of complications. Although there have been some reports on the feasibility of fertility preservation in these subsets of patients awaiting HSCT, it is of critical importance to assess continuously these outcomes to improve our ability to prepare, counsel, and develop optimal stimulation protocols.

The choice between oocyte and embryo cryopreservation is patient specific; however, oocyte cryopreservation has been chosen for patients in our program given that the majority of our cohort is young (mean age 23.7 years), unpartnered, and may feel uncomfortable with the use of donor sperm to cryopreserve embryos. Additionally, in the setting of life-threatening medical conditions, some may find oocyte disposition less emotionally and ethically challenging than embryo disposition. Oocyte to live–born child efficiency estimates provide reassurance that the use of vitrified oocytes should afford our patients similar probabilities of live birth when compared with in vitro fertilization with fresh oocytes. Doyle et al. published a retrospective evaluation of 128 autologous in vitro fertilization cycles using vitrified/warmed oocytes cryopreserved for medical and elective indications. They reported a clinical pregnancy rate of 57.1%, a live birth rate of 38.6%, and a live–born child efficiency rate of 6.4% per each warmed oocyte. Broadly applying this data to our patient cohort with an average of 9.0 oocytes cryopreserved, we could estimate the chances of one live–born child to be approximately 60%. This estimate is similar when using the predictive models the same article poses for women aged 30–34 (the youngest group modeled), which recommends cryopreserving 15–20 MII oocytes for a 70%–80% chance of at least one live birth. Given that the majority of patients examined in this study underwent oocyte cryopreservation electively, it remains questionable whether these statistics can be applied directly to a cohort of women with various diseases.

Each medical condition may have a different degree of impact on fertility potential and cryopreservation outcomes. Our study demonstrates the feasibility of oocyte cryopreservation in patients with GATA2 deficiency and DOCK8 deficiency, two rare single-gene disorders that impact immune function. GATA binding protein 2 expression has been observed in epithelial and stromal tissues of the uterus and is correlated positively with P receptor levels. Mutations in GATA2 have been hypothesized to alter P responsiveness through reducing P receptor expression, which may manifest clinically as failed embryo implantation, impaired endometrial decidualization, and uninhibited estrogen signaling. Despite these potential limitations, outcomes of COS in women with GATA2 deficiency remained reassuring and more optimistic than our prior publication. Given the relatively recent discovery of DOCK8 deficiency, fertility potential has not been studied widely in these patients. This is the first study to report successful COS in patients with this condition. Collectively, patients with DOCK8 deficiency were the youngest on average (16.5 years), which is likely reflective of young age at first symptoms, diagnosis, and referral. This also may be a function of disease severity because these patients undergo bone marrow transplantation at young ages to prevent development of malignancy. In both conditions, fertilization rates and results of subsequent embryo transfer will be important to follow.

Contributing factors to infertility in SCD may include chronic inflammation, oxidative stress, ovarian sickling, and secondary hemochromatosis as a result of repeated transfusions. A case series by Lavery et al. described eight

DISCUSSION

We described the outcomes of oocyte cryopreservation cycles in women diagnosed with DOCK8 deficiency, GATA2 deficiency, and SCD prior to HSCT. Conditioning regimens for HSCT involve high-dose chemoradiotherapy, which leads to ovarian destruction. Biopsy specimens from patients exposed to these agents show ovarian fibrosis and impairment of follicular maturation. Spontaneous conception following HSCT has been reported, but close monitoring is advised due to an increased frequency of complications. Although there have been some reports on the feasibility of fertility preservation in these subsets of patients awaiting HSCT, it is of critical importance to assess continuously these outcomes to improve our ability to prepare, counsel, and develop optimal stimulation protocols.
patients undergoing oocyte cryopreservation for SCD. They reported a slightly higher mean number of mature oocytes cryopreserved when compared with our study (12.1 vs. 10.7) despite a relatively similar duration of stimulation (11.0 days vs. 10.9 days) and higher total gonadotropin doses in our cohort. Although these differences are subtle, the older age of our patients (27.3 vs. 16.3 years) may have impacted both ovarian reserve and disease severity to a greater degree than the Lavery et al. (28) cohort. Overall, COS and subsequent cryopreservation have been achieved in patients with SCD, but disease severity and inherent risk of vaso-occlusive events and thrombosis must be appreciated (1). Any definitive conclusions are limited by our sample size, but we have been able to demonstrate the feasibility of oocyte cryopreservation in these patients.

The three complications seen in our patients were PE in a patient with GATA2 deficiency, acute pain crisis in a patient with SCD, and a patient with GATA 2 deficiency who had no mature oocytes cryopreserved. The baseline risk of venous thromboembolism (VTE) with assisted reproductive technology (ART) is approximately 0.11% (37). It is known that VTE is more likely to occur with OHSS due to high E2 levels and hemoconcentration. There are no concrete data to suggest that ART in and of itself is a risk factor (17, 38, 39). Our patient had a PE in the absence of OHSS. She had no personal or family history of VTE. Venous thromboses have been reported in 25% of patients with GATA2 deficiency; this high rate of thrombotic events in these patients may be related to the role of GATA2 in vascular development (11, 40–42). Zolton et al. (17) highlights the recommendation that patients at moderate to high risk for VTE should be on prophylactic anticoagulation at the time of ovarian stimulation. Dovey et al. (1) suggest initiation of enoxaparin on day 1 of stimulation with continuation until 24 hours prior to retrieval to prevent thromboembolic events in high-risk patients. A single-center case series and systematic review by Pecker et al. (23) suggests that the rate of SCD-related complications, including acute chest syndrome, pain crises both before and after stimulation, and bacteremia may be disproportionately high in this population when undergoing oocyte cryopreservation (1, 23, 28). This further highlights the importance of a multidisciplinary approach for patients with an elevated baseline risk for complications and the need to identify ways to decrease the risk of pain crisis and VTE. One patient with GATA2 deficiency had zero mature oocytes cryopreserved despite two stimulation attempts and overtly normal ovarian reserve parameters. This finding was seemingly an outlier in this cohort of women. Prior research has demonstrated the use of multidisciplinary treatment planning in ART results in improved oocyte retrieval success rates and decreased rates of complications during ovarian stimulation (2, 17, 23, 28).

CONCLUSION

Ovarian stimulation with subsequent oocyte vitrification in patients with GATA2 and DOCK8 deficiency and SCD can be performed successfully and safely through a multidisciplinary treatment approach. Though none of our patients have followed-up for fertilization of oocytes, discussing outcomes related to oocyte cryopreservation serves as an integral part of counselling and care in this unique population of young women facing HSCT. As this cohort is followed longitudinally, more data regarding oocyte fertilization with subsequent pregnancy outcomes can be collected and used to refine our counseling and management.

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