Journal of Assisted Reproduction and Genetics (2019) 36:1753–1756
https://doi.org/10.1007/s10815-019-01516-8

FERTILITY PRESERVATION

Oncofertility conundrum: discrepancy between anti-Müllerian hormone and mature oocyte yield in a peripubertal girl with Hodgkin lymphoma

D. Garg[1] · E. B. Johnstone[1] · D. B. Fair[1] · D. T. Carrell[1] · S. Berga[1] · J. M. Letourneau[1]

Received: 19 March 2019 / Accepted: 20 June 2019 / Published online: 15 July 2019

Introduction

Cancer is diagnosed annually in approximately 18 people per 100,000 whose age is less than 20 years in the USA [1]. Recent medical advances have improved 5-year survival rates for pediatric cancers, with a greater than 80% decrease in childhood cancer mortality [2]. In adolescents, cancer-related infertility is an important concern. Studies have shown that questions surrounding fertility preservation might affect decisions regarding cancer treatment [3]. After cancer treatment, infertility and reproductive health issues can cause significant distress in younger cancer survivors [4, 5].

Several established options for fertility preservation options are available for newly diagnosed female adolescent cancer patients, including oocyte cryopreservation and use of third-party reproduction in the future. Other options also include ovarian tissue cryopreservation and ovarian tissue reimplantation after cancer treatment [6]. In adult patients with newly diagnosed cancer, there is conflicting data regarding diminished response to ovarian stimulation [7, 8]. A recent study has demonstrated no impact of cancer diagnosis in response to ovarian stimulation [9]. Little is known about the response to ovarian stimulation among adolescents in general, and the response to ovarian stimulation in adolescent girls with newly diagnosed cancer is poorly understood. We present a case of a 14-year-old patient who sought consultation for fertility preservation shortly after being diagnosed with Hodgkin lymphoma. We include the challenges and knowledge gaps involved in the management of ovarian stimulation in adolescent patients who present for fertility preservation.

✉ D. Garg
drgargdeepika@gmail.com

[1] Department of Obstetrics and Gynecology, University of Utah, Salt Lake City, UT 84108, USA

Case presentation

A 14-year-old girl with recently diagnosed with stage IV Hodgkin lymphoma presented for a fertility preservation consultation prior to chemotherapy. Her treatment plan included chemotherapy as per the Children's Oncology Group study AHOD0031: two cycles of chemotherapy, which included doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, and prednisone (ABVE-PC) followed by response evaluation. Additional therapy could include two additional ABVE-PC cycles with or without two cycles of dexamethasone, etoposide, cisplatin, and cytarabine, with or without involved field radiotherapy [10]. Her pubertal history included regular menstrual cycles that started at age 11; she had reached her expected mean parental height of 5′ 11″, had Tanner stage 4 pubic hair development, and had recently reached Tanner stage 5 breast development. She presented on day 29 of her menstrual cycle to our infertility clinic. Her recent menstrual cycles were regular and she was not on any hormonal therapies.

The patient and her family were counseled extensively about the possible risks and benefits of the chemotherapy, including the high risk of accelerated oocyte depletion and possibility of premature ovarian insufficiency. Oocyte cryopreservation and ovarian tissue cryopreservation were discussed with the family as available options for fertility preservation. In our center, we do not currently perform ovarian tissue cryopreservation so the option for ovarian tissue cryopreservation at other regional facilities was made available. However, the patient and her family wished to proceed with oocyte cryopreservation and not ovarian tissue cryopreservation. Pre-chemotherapy serum anti-Müllerian hormone (AMH) level was found to be 0.4 ng/mL (0.2–6.3 ng/mL), indicating low ovarian reserve. Antral follicle count (AFC) with transvaginal ultrasound was performed at her initial reproductive endocrinology visit, with 11 antral follicles seen. Although our patient was virginal, she endorsed using tampons and assented to undergoing transvaginal ultrasound for follicular monitoring and oocyte retrieval.

For ovarian stimulation, a random-start, antagonist-based protocol was started on day 30 of her menstrual cycle. Ovarian stimulation was initiated with Gonal-F (recombinant follicle-stimulating hormone, EMD Serono, Inc.), 225 IU/day, and Menopur (highly purified human menopausal gonadotropins, Ferring Pharmaceuticals, NJ, USA), 150 IU/day. Routine monitoring with transvaginal ultrasound and serum estradiol levels was performed and a gradual rise in estradiol was noted being 102 pg/mL on cycle day 5, 225 pg/mL on cycle day 8, and 406 pg/mL on cycle day 10. GnRH antagonist was started on cycle day 6. On the 11th day of ovarian stimulation, there were 15 follicles below 15 mm in diameter and 11 follicles at 15 mm or greater in diameter. Her peak estradiol level was 601 pg/mL on cycle day 11. NOVAREL® 5000 units (chorionic gonadotropin, Ferring Pharmaceuticals, NJ, USA) was injected intramuscularly, and 36 h later, transvaginal oocyte retrieval was performed, yielding 13 oocytes. Eleven of the oocytes were in metaphase II at the time of oocyte retrieval and were cryopreserved.

Discussion

This case highlights several important considerations when undertaking fertility preservation in adolescent women. First, our case resulted in successful retrieval of 11 mature eggs, despite a relatively low AMH and a low estradiol level on the day of trigger. While the role of advancing age in ovarian stimulation in adult patients has been more extensively studied, ovarian stimulation in adolescents is poorly understood.

Mature oocyte cryopreservation has been a standard of care for adolescent girls who do not have a fertility partner [11, 12]. There are limited data on oocyte cryopreservation in adolescent patients and chance of subsequent live birth. However, among women aged 25–42 years, the chances of live birth following oocyte cryopreservation declined with patient age [13, 14]. Authors have reported the chance of live birth was 90%, 75%, and 37%, respectively, in patients of age 34, 37, and 42 years old with 20 mature eggs frozen [13].

Reproductive outcomes of oocyte cryopreservation depend on the quality of oocytes [15]. It is well known that oocyte quality diminishes with advancing age. However, a "J-shaped" curve of age versus aneuploidy rates has been described, with relatively higher rates of aneuploidy in both the teenage and latter reproductive years, as compared with the twenties [16]. As the hypothalamic-pituitary-ovarian axis matures, oocyte competence may improve in the latter teens and early twenties, followed by a decline that begins in the mid- to late-twenties [16]. Diminished egg quality and aneuploidy are characteristic of the earliest ovulatory cycles in post-menarchal patients, which may contribute to suboptimal reproductive outcomes for adolescent girls undergoing fertility preservation [17–19]. In the setting of oocyte cryopreservation in young adolescent patients for oncofertility, we should counsel our patients about the uncertainty of the treatment outcome.

The dynamics of ovarian follicular development in the adolescent years are complicated. Initial recruitment of ovarian follicles starts before the onset of puberty and is assumed to be a continuous process. After initial recruitment of follicles begins, development from primordial to primary and pre-antral follicles becomes prominent throughout the ovary [20]. During the peripubertal period, increasingly large cohorts of antral follicles begin to escape apoptosis due to increased follicle-stimulating hormone (FSH). FSH's rise is a result of maturation of the hypothalamic-pituitary axis, as gonadotropin-releasing hormone is released in orderly and pulsatile manner [19]. It is possible that the performance of the hypothalamic-pituitary axis could be diminished in the setting of cancer [21]. As more antral follicles begin to escape apoptosis, single dominant follicles attain faster growth, likely due to enhanced FSH receptor expression or increase sensitivity to FSH and more regular menstrual cyclicity is eventually observed [22, 23]. During the peripubertal years, there is a rise in AMH levels, indicating enhanced ovarian small antral follicle activity. This rise in AMH is followed by drop in AMH levels after puberty, due to development of small antral follicles into antral follicles, which do not produce AMH [24].

Our patient had random serum AMH level of 0.4 ng/mL, but we were able to retrieve 13 oocytes and 11 were mature that were cryopreserved. The numbers of mature oocytes retrieved and cryopreserved were in contrast to her low AMH levels. We hypothesize the combination of our patient's cancer diagnosis and her relatively recent post-pubertal status combined to make AMH less predictive of her response to ovarian stimulation. While the utility of standard markers such as AMH, AFC, estradiol, follicular size, and follicular growth has been established in adults, their utility in predicting response to ovarian stimulation in adolescents remains poorly understood [25].

The Bologna criteria for poor ovarian response utilize an AMH threshold between 0.5 and 1.1 ng/mL as being highly predictive of poor ovarian response, defined as 3 or fewer oocytes retrieved, based on review of multiple studies conducted in adult women with infertility [26]. It is unknown whether these thresholds apply to recently post-pubertal adolescents. During controlled ovarian hyperstimulation in adult non-cancer patients undergoing infertility treatment, follicles > 18 mm are most likely to have mature oocytes, with the probability of a mature oocyte 70%, 90%, and 92% less in follicles at size ranges of 13–15 mm, 10–12 mm, and < 10 mm, respectively [27]. Others have suggested that serum estradiol concentration is a better marker than follicle size for the activity of granulosa cells in a follicle and for predicting oocyte maturation [28]. Lower maximal estradiol (E2) levels at the time of oocyte retrieval were reported in adult women with cancer undergoing controlled ovarian hyperstimulation

(COH) [29]. Previous studies have shown conflicting results in cancer patients regarding ovarian response indices in COH for fertility preservation [8, 30]. The hypothalamic-pituitary-ovarian axis in these patients might be affected due to elevated stress hormones, higher catabolic state, and deficient nutrition secondary to cancer [31].

Prior studies have found significant correlation between days 1 and 3 serum AMH and mature oocytes retrieved after COH in women undergoing in vitro fertilization (IVF) [32]. The outcome of this cycle suggests that the response to ovarian stimulation for adolescent cancer patients may not be the same as in non-cancer or adult cancer patients, and this underscores the importance of assessing multiple markers to estimate oocyte maturity, including both follicle size and estradiol [27]. This patient's lower-than-average AMH prompted counseling that it was possible that very few oocytes may be retrieved. In addition, her low estradiol on the day of oocyte trigger added to the uncertainty. However, she ultimately had a mature oocyte yield that was similar to expected, based on her number of mature-size follicles and initial antral follicle count.

We considered whether the timing within her menstrual cycle of ovarian stimulation start may have also played a role in follicular dynamics and oocyte yield. This patient had ovarian stimulation started in her late luteal phase, as she needed to start her cancer treatment quickly. Random-start stimulation allows immediate initiation of ovarian stimulation and minimizes cancer treatment delay [33]. A recent study has shown that there is no difference in number of immature and mature oocytes retrieved and fertilization rates between stimulation initiated during the follicular or luteal phase of the menstrual cycle [33]. Despite the potential differences in follicle dynamics in peri-pubescent teens, random-start ovarian stimulation was still successful in this case.

Notably, in virgin adolescents, like our patient, transvaginal procedures for oocyte retrieval such as transvaginal ultrasound and transvaginal retrieval of oocyte may be difficult to accept by the patient and/or her parents. However, the decision of accepting transvaginal procedures for fertility preservation overlaps with individual beliefs and cultural priorities. Therefore, virginity may be a subject to discussion with the patient and her family and might require involvement of a psychologist to help patients to make their decision [34].

Fertility preservation in cancer patients is a rapidly expanding field and requires individualized care. An increased awareness of complexities involved in adolescent fertility preservation should help physicians improve options. This case report demonstrates that random-start oocyte cryopreservation can be successfully carried out in an adolescent cancer patient with low serum AMH. Fertility preservation should be offered to female adolescent cancer patients to improve their quality of life. Further studies are required in peripubertal and early post-pubertal cancer patients to optimize the gonadotropin dosing and protocol for ovarian stimulation and to determine the markers of egg maturity. Moreover, serum AMH and estradiol concentrations may not be predictive of the number of mature oocytes retrieved, and these should not be used to exclude adolescents from oocyte cryopreservation. While AMH is predictive for response to ovarian stimulation in infertile patients, much less is known in the fertile population as well as young adults/teens. This finding is in an isolated adolescent and may or may not be true for all adolescent patients. Especially given is that we sometimes see excellent stimulation in adult patients with poor markers of ovarian reserve.

Acknowledgments The authors thank entire staff who helped in the management of this patient.

Author's roles All authors contributed in writing this manuscript and approved before submission.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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