Chapter 21

Gynecologic and Obstetric Considerations

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Introduction

Women with dyskeratosis congenita and telomere biology disorders (DC/TBDs) may benefit from a focus on their gynecologic and reproductive health. In this chapter, we review considerations about routine gynecologic surveillance, special concerns around HCT, gynecologic conditions, fertility, prenatal diagnosis, and pregnancy and obstetric complications. A woman with DC/TBD would benefit from including a gynecologist within her clinical care team to assess her gynecologic and reproductive health.

Overview

A recent publication by Giri et al reporting on the gynecologic issues, fertility and pregnancy outcomes in 39 females with DC/TBDs after menarche suggests that though they undergo menarche and menopause at normal ages as compared to the general population, these women face several key gynecologic problems [1].

First, two thirds of the women present with hematologic symptoms with a significant proportion of those having heavy menses that remains heavy despite using hormonal contraception [1].

Second, some of these women later may undergo hematopoietic cell transplantation (HCT) to treat either bone marrow failure or malignancy. HCT has unique concerns for gynecologic and reproductive health, and may lead to early menopause or infertility for most [2]. Additionally, if a patient undergoes HCT, there is an increased risk for secondary cancers caused by the treatment and an increased risk of lower genital tract HPV disease, but the risk of cervical cancer does not appear to be increased, especially with routine surveillance and posttransplant HPV vaccination [3, 4, 5].

Third, as more women with DC/TBDs become pregnant, information is emerging about their fertility and pregnancy outcomes. Similar to women with other inherited bone marrow failure syndromes, they may have problems with fertility and a higher rate of pregnancy complications related to low blood and platelet counts [1, 6-8].

While nearly all of the women desiring childbearing became pregnant and had a liveborn child, they sometimes had to use fertility assistance to become pregnant and had a higher rate of recurrent pregnancy loss, signs of reduced fecundability [1]. Given the recently reported observations of increased risk of recurrent miscarriage, high rates of preeclampsia, and hematologic complications that can lead to increased preterm birth and primary cesarean section rates, women with DC/TBDs benefit from coordinated care by hematology, gynecology and maternal fetal medicine specialist [1].

Fourth, while women in the general population with telomere shortening are known to have a higher risk of menopause before age 40 or premature ovarian insufficiency and infertility, the recent study of women with DC/TBDs, however, shows natural menopause at a median age of 49 years [1, 9]. Women generally survive into their 50s, underscoring the importance of obtaining necessary screening tests and exams throughout the reproductive years [10]. Though women with DC/TBDs have an increased risk of all types of malignancy, the overall risk of gynecologic cancer does not appear to be increased [3].

Menarche

Women with DC/TBDs attained menarche at normal ages (median 12 years; range 9-17), similar to the general population [1]. Most females begin menarche between the ages of 11 to 16 years, approximately three years after the thelarche, or when the breast buds develop [11]. As can be seen in other bone marrow failure syndromes and chronic disease, young girls may experience pubertal delay due to low body weight, chronic disease, or after HCT. The body requires sufficient body mass and endocrine hormonal signaling to begin menarche. Hormonal signaling can be interrupted by chronic illness and medications, such as oxymetholone (a synthetic anabolic steroid) used in cytopenia. If menses do not occur within 3 years after breast buds develop or by age 16, evaluation by an adolescent medicine specialist or pediatric endocrinologist is warranted [12].

Human Papillomavirus and Cervical Cancer Screening

Human papillomavirus (HPV) is a sexually transmitted virus which can affect squamous cells in the genital area and is associated with genital warts, lower genital tract precancer, and cancer, and oropharyngeal cancer. The currently recommended vaccine licensed by the U.S. Food and Drug Administration (FDA) for prevention of HPV infection is Gardasil9®. The Gardasil9® vaccine prevents nine types of HPV: types 16, 18, 31, 33,

45, 52, and 58 which are associated with 90% of cervical cancer, and types 6 and 11, which cause 90% of genital warts [13]. The vaccine is currently FDA approved for girls/women and boys/men ages 9-45 years [14]. Individuals receive a three-injection series if age 15 years or older, with the subsequent shots given 2 and 6 months after the first, and a two-injection series for girls and boys younger than 15 years, with the second shot given 6-12 months after the first dose [15]. It is not known whether individuals with TBDs or bone marrow failure should receive the three- rather than the two-injection series, but generally those with potentially impaired immunity receive a three-injection series. Adults ages 27 through 45 years who have not been vaccinated may decide to get the HPV vaccine after speaking with their health care provider about their risk of new HPV infections and the possible benefits of vaccination. Vaccination has the greatest benefit if completed prior to the onset of sexual activity.

Abnormal Pap smears and HPV tests are managed by using established guidelines for evaluation and treatment [16]. Patients with an abnormal Pap smear or positive HPV test undergo a procedure called colposcopy, where a clinician, usually a gynecologist, takes a closer look at the cervix and biopsies any areas that appear abnormal. At the time of colposcopy, the vagina and vulva are inspected for other lesions which, if noted, are routinely biopsied as well. Any woman who has biopsy findings of moderate dysplasia or worse warrants treatment. Counseling regarding safe sex practices may help limit exposure to sexually transmitted infections and is important given the impaired immune response in many women with DC/TBDs.

Screening and early detection of lower genital tract squamous cell abnormalities like precancer enables less invasive and successful treatment. The current recommendation for women is to start yearly comprehensive gynecologic exams when they become sexually active or at age 21 [16, 17]. It is reasonable to recommend that women with DC/TBDs have yearly cervical cancer screening especially those with any immune impairment [18]. Additionally, after HCT, annual screening and HPV vaccination is advised [2].

Menstrual Bleeding

Two thirds of the women with DC/TBDs develop hematologic symptoms with a significant proportion of those having heavy menses; despite using hormonal contraception, heavy menses continues in some [1]. Endometriosis is also reported in women with DC/TBDs and is associated with heavy menses. As part of the evaluation of excessive menstrual bleeding in any woman, a complete blood count and pregnancy testing are assessed. An ultrasound may be helpful to exclude other causes of excessive menstrual bleeding including ovarian cysts, or polyps or submucosal fibroids that may form within the uterine cavity.

Mild to moderate menstrual bleeding can usually be controlled with low dose combined oral contraceptives (35 mcg or less of ethinyl estradiol) rather than using high dose estrogen containing pills. These higher dose pills have an increased risk of endometrial atrophy or thinning of the lining of the uterus, which can lead to excessive bleeding with long term use [19, 20]. Heavy menstrual bleeding in the setting of severe thrombocytopenia or bone marrow failure warrants management with hormonal therapy in addition to platelet support. Androgens, commonly oxymetholone or danazol, may be used to treat cytopenia in DC/TBDs (see Chapter 22, Endocrine and Skeletal Disorders).

Patients should have thorough discussions with their care team regarding family planning while on androgens.

Management of Gynecologic Issues During HCT

Approximately 10-30% of DC/TBDs patients undergo HCT for either bone marrow failure or malignancy [1, 3]. Hormonal therapy eliminated symptoms in 97% of patients seen for excessive menstrual bleeding during HCT performed for a variety of indications. Of these women, a single oral contraceptive regimen was effective in 79% [19]. Low dose contraceptives can be given in a transdermal patch, especially in women with poor oral tolerance and elevated liver enzymes [2]. In cases of severe bleeding, high dose oral

contraceptives containing 50 mcg or higher of ethinyl estradiol, or injectable estrogens (intravenous premarin 25 mcg every 6 hours for 24 hours) can be used. These higher doses are maintained until bleeding stops and then treatment is switched to a form of medication that can be continued long-term, such as low dose combined oral contraceptives, or leuprolide acetate [2].

Another class of medications called gonadotropin releasing hormone (GnRH) agonists such as leuprolide acetate, is given by intramuscular injection and has been shown to be effective in suppression of menses in women scheduled for transplant [2]. Injections may, however, be relatively contraindicated in some patients with severe thrombocytopenia because of the risk of bruising or bleeding at the injection site. Patients who experience intolerable hypoestrogenic side effects such as hot flashes or vaginal dryness with leuprolide acetate may benefit from additional treatment with hormone replacement such as low dose combined oral contraceptives.

Patients who have premature ovarian insufficiency, defined as menopause before age 40, that frequently arises from radiation and chemotherapy of HCT may benefit from starting hormone replacement with estrogen and progestins to reach full bone density and maintain sexual function. There are two options in hormone replacement: low dose combined hormonal contraceptives or hormone replacement therapy (HRT), which usually contains lower amounts of hormones than contraceptive preparations. If a woman undergoes premature ovarian failure from HCT before age 35, she may benefit from combined hormonal contraceptives containing at least 30 mcg of ethinyl estradiol to ensure prevention of pregnancy and to maintain bone mass. It has been shown in the general population that women with premature ovarian failure who do not use HRT have increased rates of illness and death compared to women who used HRT [21]. Hormone replacement may help women feel more like their peers and maintain psychological and sexual health.

After HCT, annual cervical cancer screening is advised because of an increased risk of HPV-related disease and to prevent the risk of developing genital tract squamous cell

cancers [22]. Revaccination with HPV vaccine may be considered as an additional strategy to decrease the risk of HPV-related neoplasia [5]. Genital graft-versus-host disease may result in genital scarring in some. Given prior reports of urethral stenosis in DC/TBDs, it is not clear whether the scarring is due, in part, to underlying DC/TBDs (see Chapter 20, Genitourinary Complications) [23, 24]. Other secondary cancers may arise as a result of treatment, because of reactivation of viruses or because the individual has other risk factors for cancers [2, 3, 22].

Fertility and Pregnancy Complications

Recent reports on women with DC/TBDs have expanded the understanding of fertility in this population. Though a small cross-sectional study showed low Anti-Mullerian hormone (AMH) levels in women with DC/TBDs indicative of low ovarian reserve [25], a more recent longitudinal report demonstrates that 25 of 26 women with DC/TBDs who were trying to conceive delivered a live baby illustrating that these women are fertile but experience reduced fecundability [1]. Most of these women in this study who gave birth had a variant in an AD inherited gene other than *TINF2*. Thirteen others in this cohort of 39 women with DC/TBDs had mutations in genes that were either not inherited (*de novo*), AR inheritance, or unknown gene and were less likely to give birth. These women were more likely to have disease-related morbidity that took precedence over family building or were of younger age.

Women with DC/TBDs appear to be at increased risk of pregnancy complications such as recurrent miscarriage, preeclampsia, preterm delivery, increased cesarean delivery rates, maternal transfusion because of low platelet counts, and an increase in postpartum hemorrhage [1]. Because of the increased risks of preeclampsia or worsening bone marrow failure during pregnancy, consultation with a maternal fetal medicine specialist to closely monitor the health of the mother and baby is an important aspect of prenatal care. Serial monitoring of hematologic parameters during pregnancy is warranted to decrease the risk of adverse maternal or fetal outcomes. Based on this

recent study, it appears that bone marrow failure that worsens during pregnancy generally resolves after delivery.

Menopause

In the United States, the average age of menopause within the general population is around 51 years, ranging anywhere from 40-61. Women with DC/TBDs had natural menopause at median age of 49 years (range 46-52) with some undergoing surgical menopause related to endometriosis, uterine prolapse or cervical precancer [1]. Women with telomere shortening as part of ovarian aging appear to be at higher risk of premature ovarian insufficiency [9] though this association has not been consistently reported in women with DC/TBDs. Additionally, women with DC/TBDs who are taking androgens during the transition to menopause may not experience any menopausal signs or be aware that they have experienced menopause.

Options for Family-Building: Cancer Treatment and Fertility

Any woman undergoing cancer treatments or HCT benefits from having discussions with the care team about the potential effect of these treatments on fertility. In some cases, fertility preservation may be possible prior to initiating cancer treatments [2, 26, 27], as reported in the recent study by Giri et al [1]. This process requires evaluation and discussion of the choices with a reproductive endocrinologist or fertility specialist. As part of shared-decision making, there are other family-building options to consider including egg donation, surrogacy, and adoption that are covered in the genetic counseling chapter.

Assisted reproductive technologies (ART), such as in vitro fertilization, to achieve oocyte or embryo cryopreservation independent of HCT, may also be considered by women

with DC/TBDs to enable family building. This technology allows for genetic testing in the embryos. This testing, called pre-implantation genetic diagnosis (PGD), is discussed elsewhere in this book (see Chapter 5, The Genetics of Dyskeratosis Congenita and Telomere Biology Disorders). Importantly, ART does not ensure fertility nor will it protect against miscarriage. As TBDs remain lethal diseases in many women, part of shared decision-making regarding fertility preservation may include discussing posthumous disposition of cryopreserved oocytes and embryos.

Malignancy Risk

Individuals with DC/TBD are at increased risk of squamous cell carcinoma [28]. While anogenital cancers in men with DC/TBDs have been reported, to date, only one case of cervical cancer was reported in women with DC [3].

Breast Cancer

There are currently no published reports of increased risk of breast cancer in women with DC/TBDs. Therefore, breast cancer surveillance can conform to the recommendations for otherwise healthy women which includes mammograms and breast exams annually starting at age 40 [29].

Future Research

Although understanding of DC/TBDs has grown tremendously in the past decade, there is still a need for further research to be completed. Main areas of research include further characterization of how telomere biology affects the obstetrical and gynecologic health of women with DC/TBDs and understanding the relationship between DC/TBDs and cancer in women. Further information is also needed on the safety and immunogenicity of HPV vaccination in women with DC/TBDs.

References

1. Giri N, Alter BP, Savage SA, Stratton P. Gynaecological and reproductive health of women with telomere biology disorders. *Br J Haematol*. 2021;193(6):1238-1246.
2. Murphy J, McKenna M, Abdelazim S, Battiwalla M, Stratton P. A Practical Guide to Gynecologic and Reproductive Health in Women Undergoing Hematopoietic Stem Cell Transplant. *Biol Blood Marrow Transplant*. 2019;25(11):e331-e343.
3. Alter BP, Giri N, Savage SA, Rosenberg PS. Cancer in the National Cancer Institute inherited bone marrow failure syndrome cohort after fifteen years of follow-up. *Haematologica*. 2018;103(1):30-39.
4. Shanis D, Anandi P, Grant C, et al. Risks factors and timing of genital human papillomavirus (HPV) infection in female stem cell transplant survivors: a longitudinal study. *Bone Marrow Transplant*. 2018;53(1):78-83.
5. Stratton P, Battiwalla M, Tian X, et al. Immune Response Following Quadrivalent Human Papillomavirus Vaccination in Women After Hematopoietic Allogeneic Stem Cell Transplant: A Nonrandomized Clinical Trial. *JAMA Oncol*. 2020;6(5):696-705.
6. Alter BP, Kumar M, Lockhart LL, Sprinz PG, Rowe TF. Pregnancy in bone marrow failure syndromes: Diamond-Blackfan anaemia and Shwachman-Diamond syndrome. *Br J Haematol*. 1999;107(1):49-54.
7. Gansner JM, Achebe MM, Gray KJ, et al. Pregnancy outcomes in inherited bone marrow failure syndromes. *Blood*. 2017;130(14):1671-1674.
8. Giri N, Stratton P, Savage SA, Alter BP. Pregnancies in patients with inherited bone marrow failure syndromes in the NCI cohort. *Blood*. 2017;130(14):1674-1676.
9. Keefe DL. Telomeres, Reproductive Aging, and Genomic Instability During Early Development. *Reprod Sci*. 2016;23(12):1612-1615.
10. Alter BP, Giri N, Savage SA, et al. Malignancies and survival patterns in the National Cancer Institute inherited bone marrow failure syndromes cohort study. *Br J Haematol*. 2010;150(2):179-188.
11. ACOG Committee Opinion No. 651: Menstruation in Girls and Adolescents: Using the Menstrual Cycle as a Vital Sign. *Obstet Gynecol*. 2015;126(6):e143-e146.
12. Fenichel P. Delayed puberty. *Endocr Dev*. 2012;22:138-159.
13. Petrosky E, Bocchini JA Jr, Hariri S, et al. Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory

committee on immunization practices. *MMWR Morb Mortal Wkly Rep*. 2015;64(11):300-304.

14. U.S. Food and Drug Administration. FDA Approves Expanded Use of Gardasil 9 to Include Individuals 27 Through 45 Years Old. *U.S. Food and Drug Administration*, Oct. 2018, www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm622715.htm.

15. Markowitz LE, Meites E, Unger ER. Two vs Three Doses of Human Papillomavirus Vaccine: New Policy for the Second Decade of the Vaccination Program. *JAMA*. 2016;316(22):2370-2372.

16. Massad LS, Einstein MH, Huh WK, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *Obstet Gynecol*. 2013;121(4):829-846.

17. Moyer VA; U.S. Preventive Services Task Force. Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement [published correction appears in Ann Intern Med. 2013 Jun 4;158(11):852. Ebell, Mark [added]]. *Ann Intern Med*. 2012;156(12):880-W312.

18. Savage SA, Dokal I, Armanios M, et al. Dyskeratosis congenita: the first NIH clinical research workshop. *Pediatr Blood Cancer*. 2009;53(3):520-523.

19. Amsterdam A, Jakubowski A, Castro-Malaspina H, et al. Treatment of menorrhagia in women undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2004;34(4):363-366.

20. Milroy CL, Jones KP. Gynecologic care in hematopoietic stem cell transplant patients: a review. *Obstet Gynecol Surv*. 2010;65(10):668-679.

21. Parker WH, Feskanich D, Broder MS, et al. Long-term mortality associated with oophorectomy compared with ovarian conservation in the nurses' health study. *Obstet Gynecol*. 2013;121(4):709-716.

22. Shanis D, Anandi P, Grant C, et al. Risks factors and timing of genital human papillomavirus (HPV) infection in female stem cell transplant survivors: a longitudinal study. *Bone Marrow Transplant*. 2018;53(1):78-83.

23. Shimamura A, Alter BP. Pathophysiology and management of inherited bone marrow failure syndromes [published correction appears in Blood Rev. 2010 Jul-Sep;24(4-5):201]. *Blood Rev*. 2010;24(3):101-122.

24. Niewisch MR, Savage SA. An update on the biology and management of dyskeratosis congenita and related telomere biology disorders. *Expert Rev Hematol*. 2019;12(12):1037-1052.

25. Sklavos MM, Stratton P, Giri N, Alter BP, Savage SA, Pinto LA. Reduced serum levels of anti-Müllerian hormone in females with inherited bone marrow failure syndromes. *J Clin Endocrinol Metab*. 2015;100(2):E197-E203.

26. Noyes N, Labella PA, Grifo J, Knopman JM. Oocyte cryopreservation: a feasible fertility preservation option for reproductive age cancer survivors. *J Assist Reprod Genet*. 2010;27(8):495-499.

27. Ethics Committee of American Society for Reproductive Medicine. Fertility preservation and reproduction in patients facing gonadotoxic therapies: a committee opinion. *Fertil Steril*. 2013;100(5):1224-1231.

28. Bessler M, Wilson DB, Mason PJ. Dyskeratosis congenita. *FEBS Lett*. 2010;584(17):3831-3838.

29. Practice Bulletin Number 179: Breast Cancer Risk Assessment and Screening in Average-Risk Women. *Obstet Gynecol*. 2017;130(1):e1-e16.