HHS Public Access

Author manuscript

Gynecol Oncol. Author manuscript; available in PMC 2021 March 01.

Published in final edited form as:

Gynecol Oncol. 2020 March ; 156(3): 647–653. doi:10.1016/j.ygyno.2019.12.037.

Gynecologic and Reproductive Health in Patients with Pathogenic Germline Variants in *DICER1*

Melissa A. Merideth, MD, MPH[1], **Laura A. Harney, RN, BSN**[2], **Nina Vyas, MD**[3], **Averyl Bachi, MBBS**[4], **Ann Garrity Carr, MS, CGC**[2], **D. Ashley Hill, MD**[5,6,7], **Louis P. Dehner, MD**[8], **Kris Ann P. Schultz, MD**[6,7,9], **Douglas R. Stewart, MD**[10], **Pamela Stratton, MD**[11]

[1].National Human Genome Research Institute, National Institutes of Health, Dpt. Health & Human Services, Bethesda, MD, 20892

[2].Westat, Rockville, MD, 20850

[3].Department of Obstetrics and Gynecology, University of California, Los Angeles, Los Angeles, CA 90095

[4].Department of Obstetrics and Gynaecology, Royal Surrey County Hospital, Guildford, United Kingdom GU2 7XX

[5].Department of Pathology, Center for Cancer and Immunology Research, Children's National Medical Center, Washington D.C. 20010

[6].International Pleuropulmonary Blastoma/*DICER1* Registry, Children's Minnesota, Minneapolis, MN, 55404

[7].International Ovarian and Testicular Stromal Tumor Registry, Children's Minnesota, Minneapolis, MN, 55404

[8].Division of Anatomic and Molecular Pathology, Lauren V. Ackerman Laboratory of Surgical Pathology, Barnes-Jewish and St. Louis Children's Hospitals, Washington University Medical Center, St. Louis, MO 63110

[9].Cancer and Blood Disorders Program, Children's Minnesota, Minneapolis, MN, 55404, USA

[10].Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, 20850

Corresponding Author: Melissa A. Merideth, MD, MPH; 10 Center Drive-MSC 1851, Bdg 10/10C103, Bethesda, MD 20892-1851; Work Phone 301-402-1816; Cell Phone 301-547-1906; Fax 301-480-2435; mmeridet@mail.nih.gov.

Author Contribution:

- Substantial contribution to the study conception and design, data acquisition, analysis, and interpretation - all authors.
- Drafting (MM, PS, DS) or revising (all the rest of the authors) the article for intellectual content.
- Approval of the final version – all authors.
- Agreement to be accountable for all aspects of the work related to the accuracy or integrity of any part of the work - all authors.

Conflicts of interest: Dr. Hill is owner of ResourcePath LLC, a private company with a mission to develop liquid biopsy diagnostics for rare cancers which includes *DICER1*-related cancers described in this work. None of the diagnostics under development are discussed in this work. Dr. Stewart provides contract telegenetics services to Genome Medical, Inc.

[11.]Office of the Clinical Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, 20892

Abstract

Objective: Germline pathogenic variation in *DICER1* underlies a tumor-predisposition disorder with increased risk for cervical embryonal rhabdomyosarcoma and ovarian sex-cord stromal tumors, particularly Sertoli-Leydig cell tumors. The gynecologic and reproductive health of these females has not yet been described.

Methods: All female subjects recruited from November 2011 to July 2018 participating in an epidemiologic study of families with pathogenic *DICER1* germline variation were included in this cross-sectional analysis. Participant evaluation included obstetric-gynecologic history, physical examination, hormone testing, pelvic ultrasound and record review.

Results: Of 64 females aged 2–72 years, fifteen underwent treatment for pleuropulmonary blastoma as children and three were treated for cervical embryonal rhabdomyosarcoma. Of nine patients reporting a history of ovarian tumors, all presented with virilization or amenorrhea; eight occurred in adolescence. Post-pubertal females with no history of ovarian tumors experienced normal pubertal development, reported regular menstrual cycles, were fertile and underwent natural menopause at median age of 52 years. Thirty-two of 33 women who tried to conceive successfully delivered liveborn children. Of these 32, 10 experienced pregnancy-related thyroid enlargement resulting in thyroidectomy within one year of pregnancy; nine others had undergone pre-pregnancy thyroidectomy.

Conclusion: In these *DICER1*-carrier females, *DICER1*-related gynecological tumors occurred during childhood or adolescence in some after which women generally experienced healthy reproductive lives. Individual education and screening for these tumors is warranted. The high rate of *DICER1*-related multinodular goiter resulting in pre- and post-pregnancy thyroidectomy underscores the importance of thyroid monitoring during pregnancy to ensure maternal and fetal wellbeing.

Keywords

cervical embryonal rhabdomyosarcoma; *DICER1*-related multinodular goiter; ovarian sex-cord stromal tumors; pleuropulmonary blastoma; Sertoli-Leydig cell tumors of the ovary

INTRODUCTION

Individuals who harbor germline pathogenic variants in *DICER1* (MIM #601200) have an increased risk for a variety of benign and malignant tumors. The hallmark cancer of the autosomal dominant disorder, pleuropulmonary blastoma, is one of several neoplasms that may affect children and young adults. *DICER1*-related gynecologic cancers include ovarian sex-cord stromal tumors, particularly Sertoli-Leydig cell tumors and gynandroblastomas often presenting during adolescence and embryonal rhabdomyosarcoma of the uterine cervix in children and adolescents(1, 2). Other clinical features include more common problems such as multinodular goiter, cystic nephroma, and differentiated thyroid carcinoma as well as less common entities like nasal chondromesenchymal hamartoma, ocular

medulloepithelioma, pineoblastoma, pituitary blastoma, Wilms tumor and renal sarcoma (1, 3–12).

The increased risk of neoplasms is associated with heterozygous germline pathogenic variants in *DICER1*, a gene which encodes an endoribonuclease crucial to processing microRNAs and is the first tumor predisposition disorder known to be caused by altered microRNA biogenesis(7). The pleuropulmonary blastoma locus was mapped to chromosome 14q using linkage analysis in families with multiple cases of pleuropulmonary blastoma, resulting in the identification of heterozygous germline variants in *DICER1*(7). Health care providers may consider the presence of *DICER1* pathogenic variants when a female presents with a personal or family history of ovarian sex cord-stromal tumor (especially Sertoli-Leydig cell tumor, gynandroblastoma or tumors with a variable morphologic appearance that are difficult to classify), genitourinary sarcoma or other established *DICER1* associations such as macrocephaly or multinodular goiter at a young age(13, 14). Likewise, a prenatal ultrasound showing a fetal lung cyst may suggest the presence of a *DICER1* mutation and prompt a careful maternal and paternal family history. In these circumstances, the genetic evaluation of an individual and her family should be considered.

As affected females with germline pathogenic variants in *DICER1* (hereafter, *DICER1*-carriers) are at risk of developing gynecologic tumors, we sought to describe the presenting symptoms, age, treatment, and effects of these *DICER1*-related tumors. We also hypothesized that *DICER1*-carrier females might 1) differ in the age at puberty or menarche, or report irregular menstrual cycles compared to the general population; 2) report peripubertal gynecologic issues due to *DICER*-related tumors; 3) experience adverse effects on their gynecologic and reproductive health after surviving a pediatric *DICER1*-related tumor 4) display abnormal Tanner staging, an atypical cervical appearance, an atypical pattern of reproductive hormone levels or other endocrine disorders compared to the general population; 5) might be less fertile, have a higher rate of recurrent pregnancy loss, or adverse pregnancy outcomes; 6) experience a higher rate of gynecologic diseases or a difference in age of menopause. We sought to determine whether antenatal diagnosis of affected fetuses might occur in offspring of *DICER1*-carrier women. We evaluated the gynecologic and reproductive health of a large group of thoroughly phenotyped *DICER1*-carrier females.

MATERIALS AND METHODS:

Participants (and/or their guardians for those < 18 years) provided written informed consent and were evaluated at the National Institutes of Health (NIH) Clinical Center as part of an Institutional Review Board-approved Natural History protocol, 11-C-0034 (ClinicalTrials.gov Identifier: NCT01247597). This study recruits subjects with known *DICER1*-related tumors (generally pleuropulmonary blastoma but also ovarian Sertoli-Leydig cell tumors and cystic nephroma) and their family members, as previously described (15). All females recruited from November 2011 to July 2018 with germline pathogenic *DICER1* variants were included in this analysis. Those with *DICER1*-associated tumors but who lacked pathogenic germline *DICER1* variants (putative mosaic *DICER1* or tumor-confined variants) were excluded. Pathologic materials and associated medical records were

systematically obtained on all participants and were centrally reviewed by study pathologists.

The general obstetric/gynecologic history was reviewed for all participants with emphasis on presenting symptoms, occurrence and treatment for *DICER1*-related tumors, especially gynecologic tumors, the timing of puberty, menarche and menopause, description of menstrual cycle duration and occurrence of symptoms of virilization as the primary outcomes of interest. For this paper, multinodular goiter included self-report and study ultrasound findings of any thyroid nodule rather than more stringent criteria of thyromegaly and multiple solid nodules used in our previous report(15). Antenatal and birth history was obtained for children and younger women. For women of reproductive age, fertility-infertility status, antenatal history and assessment, and pregnancy outcomes were reviewed as additional outcomes of interest. Transvaginal or abdominal pelvic ultrasound was obtained on all *DICER1*-carriers to assess for current ovarian or cervical tumors. Measured reproductive hormones included follicle-stimulating hormone, luteinizing hormone, prolactin, estradiol, inhibin A and B, 17-OH progesterone, androstenedione, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and free/total testosterone and were compared to normal ranges. Reproductive tumor markers included β-hCG tumor marker, carcinoembryonic antigen and alpha-fetoprotein (AFP).

In January 2013, anti-Müllerian hormone was added to the laboratory testing performed through the NIH Clinical Center laboratory. Those *DICER1*-carrier patients seen prior to that time had anti-Müllerian hormone testing at home when possible (n=8). For analysis of anti-Müllerian hormone levels, only those aged 16 to 45 years with both ovaries who had undergone menarche were included. Menstrual cycle regularity defined as those occurring every 21–35 days by patient history was assessed for women of reproductive age. Gynecologic physical examination evaluated for signs of virilization and Tanner staging to characterize cohort-wide abnormalities. Females > 12 years with a cervix underwent speculum and bimanual examination to determine whether the cervix appeared normal in size and shape as an outcome of interest. Assent for pelvic exam was obtained for all post-pubertal adolescents < 18 years. Medical records were obtained whenever possible to confirm diagnoses and data abstracted.

RESULTS

Puberty/menarche and menstrual history

Sixty-four *DICER1*-carrier female patients from 32 predominantly non-Hispanic white families were confirmed to have a heterozygous germline *DICER1* pathogenic variant and ranged in age from 2–72 years (median: 31 years). Of these, 15 *DICER1*-carriers were age 11 years or younger, 38 were aged 12–50 years, and 11 were over age 50 years. Three females including one adolescent with a history of embryonal rhabdomyosarcoma and one woman who had recently undergone miscarriage did not undergo speculum exam; one other adolescent refused gynecology visit altogether but underwent study laboratory testing. The mean age of menarche was 12.7 years (range 10–16 years), the same as the general population (16, 17). Those patients who survived pleuropulmonary blastoma, developed embryonal rhabdomyosarcoma, or developed ovarian Sertoli-Leydig cell tumors also had a

similar age of menarche. No patient reported precocious puberty and most reported regular menstrual cycles with normal flow.

Peripubertal gynecologic issues due to *DICER1*-related tumors

Peripubertal gynecologic issues included embryonal rhabdomyosarcoma of the cervix (n=3; table 1), ovarian Sertoli-Leydig cell tumor (SLCT) (n=1), and unilateral, asymmetric breast development (n=1). Two patients with embryonal rhabdomyosarcoma of the cervix presented with vaginal bleeding prior to menarche and vaginal mass which was described as a “grape-like mass” protruding from the vagina in one. The third patient presented with heavy vaginal discharge two years after menarche. Pathologic evaluation of all three tumors revealed embryonal rhabdomyosarcoma of the cervix, botryoid type; initial treatment for each patient included chemotherapy and vaginal trachelectomy. One of these patients whose initial tumor was diagnosed at age 7 years, developed recurrence at age 12 years which was successfully treated with surgical resection, chemotherapy and vaginal vault brachytherapy. This patient subsequently was diagnosed with an ovarian Sertoli-Leydig cell tumor at age 18 years. An individual with post-pubertal embryonal rhabdomyosarcoma ultimately underwent a hysterectomy for treatment of local disease. One individual who experienced asymmetric breast development during puberty had undergone chest radiotherapy for pleuropulmonary blastoma at age 2 years; she was treated with breast augmentation and contralateral breast reduction.

Effect of other *DICER1*-related tumors on gynecologic and reproductive health

In these females, 15 of 64 *DICER1*-carriers had a history of pleuropulmonary blastoma requiring surgical resection. All of these presented under age eight years, of whom 11 were age three years or younger. Despite 11 of 15 children being treated with a combination of surgical resection and chemotherapy with or without radiation (four with radiation versus seven without), those who were adolescents or older had an age of menarche similar to the general population(18).

DICER1-related ovarian tumors

Of nine individuals with a history of *DICER1*-related ovarian tumors, five initially had Sertoli-Leydig cell tumors, two had gynandroblastomas and two were of unknown tumor type as their pathology specimens could not be centrally reviewed. Eight occurred in adolescence (median age 16 years: range 8.5–18.3). All nine women presented with virilization and/or amenorrhea (Table 2). Two of these individuals developed a metachronous Sertoli-Leydig cell tumor in the contralateral ovary 6 and 46 years after their original diagnosis (Table 2). A small asymptomatic ovarian carcinoid tumor was identified in a third woman when she underwent laparoscopic hysterectomy and contralateral oophorectomy three months after oophorectomy for ovarian Sertoli-Leydig cell tumor. The relationship of the carcinoid to *DICER1* remains unclear. Treatment of all nine individuals comprised unilateral oophorectomy of the affected ovary with three of nine having chemotherapy treatment (age 14, 16, and 61 years). Five of these women bore children (one before and four after). One woman who also had prior cervical embryonal rhabdomyosarcoma treated with chemotherapy and low-dose brachytherapy had primary

infertility. Three others have not yet attempted childbearing including one who underwent bilateral oophorectomy before age 25 years.

Tanner staging, cervical appearance, reproductive hormone levels, and other endocrine disorders

All 64 *DICER1*-carriers had a female phenotype and normal Tanner staging for age. Of 40 individuals with a cervix who underwent pelvic examinations, all but one had a normal-appearing cervix; the one exception had mild unilateral vaginal scarring after two surgical resections of embryonal rhabdomyosarcoma and vaginal brachytherapy. Male hormone testing including DHEA, DHEAS, androstenedione, 17-OH progesterone and free/total testosterone were elevated in 9 women; none had evidence of a gynecologic tumor at time of exam (Table 3). Four of these nine women had prior diagnosis of polycystic ovarian disease (PCOS) based on standard criteria(19). One woman who also had PCOS, had signs of virilization and amenorrhea. Generally, follicle-stimulating hormone, luteinizing hormone, estradiol, prolactin, inhibin A and B, carcinoembryonic antigen, AFP, and tumor β-hCG were in the normal range and appropriate for age. All *DICER1*-carrier females over age 16 years were diagnosed with multinodular goiter (n=42) or well-differentiated thyroid carcinoma (n=4, ages 13, 20, 30, 41). Of these, 25 of 46 (54.3%) women have undergone partial or complete thyroidectomy at a median age of 20 years (range 12–60) and thus needed thyroid hormone replacement.

Reproductive outcomes

Thirty-two of 33 *DICER1*-carrier women who tried to conceive successfully delivered liveborn children. Six of these 33 reported a history of infertility with three undergoing in vitro fertilization for male factor infertility. Nine women had their first pregnancy after thyroidectomy as adolescents or young adults. These 32 women conceived a total of 111 pregnancies (median 3.0, range 1–9). Four (3.6%) pregnancies ended in first trimester termination, one (0.9%) was an ectopic pregnancy, and 23 (20.7%) resulted in spontaneous miscarriage, 21 in the first trimester and two in second trimester. Of 83 completed pregnancies (median 3, range 1–5), 71 (85.5%) resulted in vaginal deliveries and 12 (14.5%) in Cesarean births. Four (4.8%) pregnancies resulted in preterm delivery. Because of known maternal *DICER1*-carrier status, an asymptomatic lung tumor was diagnosed at 3 months in a newborn, enabling early diagnosis of pleuropulmonary blastoma prior to developing symptoms(20). This child is now doing well. In a second woman, a cystic lung lesion was detected by fetal ultrasound at 38 weeks, monitored postnatally and a pleuropulmonary blastoma was resected in the child at age three months. No other abnormalities in prenatal screening were reported. Ten women underwent thyroid surgery soon after pregnancy for enlarged thyroid and thyroid nodules, only one had thyroid carcinoma. Other complications of pregnancy were uncommon (Table 4).

Gynecologic outcomes

Of those who were post-menarche, seven women reported dysmenorrhea, two had endometriosis. Of 26 *DICER1*-carrier women aged 16 to 45 with both ovaries and available testing, anti-Müllerian hormone levels were lower than expected (median 2.94: range 0.2–10); in general, these women were fertile despite these lower anti-Müllerian hormone levels.

Nine women had undergone natural menopause at a median age of 52 years (45–53) and two others had surgical menopause. Six other women had undergone hysterectomy for various benign indications including three with leiomyomata with menorrhagia (n=2) or post-menopausal bleeding (n=1), and one each with postpartum hemorrhage, endometriosis and post-menopausal endometrial polyp. One woman had breast cancer at age 29 years: a HER2+ ductal carcinoma in situ was surgically treated by mastectomy followed by breast reconstruction and neoadjuvant chemotherapy.

DISCUSSION:

Among these 64 girls and women with germline pathogenic *DICER1* variation, nine women had a history of ovarian Sertoli-Leydig cell tumors or gynandroblastoma; three had a history of cervical embryonal rhabdomyosarcoma. Fifteen are survivors of pleuropulmonary blastoma that included surgical resection and often also included subsequent chemotherapy and radiation. Some females had a history of two different *DICER1*-related tumors. Ovarian tumors generally presented with virilization and amenorrhea during adolescence. Metachronous ovarian tumors developed later in three individuals. Among all female *DICER1*-carriers, including those with a unilateral ovarian tumor, pubertal development, menarche, and menopause occurred at the same age as the general population.(18, 21) Peripartum diagnosis of an affected fetus was facilitated by known maternal *DICER1* status. Adult women experienced a high rate of thyroid disease resulting in thyroidectomy. Thyroid disease often worsened around pregnancy and included an increased risk of thyroid cancer.

Thirty-two of 33 *DICER1*-carrier women who desired childbearing had at least one liveborn child and the rate of miscarriage was similar to the general population(22). Prior to attempting pregnancy, one female underwent hysterectomy, and another underwent bilateral oophorectomy. In those undergoing only unilateral oophorectomy, subsequent fertility was not compromised. Nearly all liveborn pregnancies continued to term and pregnancy complications were rare. Known maternal *DICER1* status enabled peripartum diagnosis of an asymptomatic pleuropulmonary blastoma in one.

Post-pubertal females who had not developed ovarian tumors generally had normal hormone levels and experienced normal menstrual cycles suggesting normal ovarian function. Of 9 *DICER1*-carrier women with mildly elevated androgens, four had PCOS, one of whom had virilization. No one had ultrasound findings suggestive of a newly diagnosed tumor. Those adolescents and adult women without rhabdomyosarcoma history had a normal-appearing uterine cervix. Anti-Müllerian hormone levels, a marker of ovarian reserve, may be lower in these otherwise fertile women. Low AMH levels have been reported in women prior to and after chemotherapy, other cancer predisposition disorders, and the general population(23–28). These reproductive-aged *DICER1*-carriers did not appear to have any risk factors for lower AMH levels. This finding may warrant investigation.

Thyroid abnormalities occurred in all females over age 16 years with a significant number undergoing thyroidectomy before or within a year of childbearing resulting in thyroidectomy among 59% of the childbearing-aged women. This high rate of *DICER1*-related multinodular thyroid disease is much higher than the 6% rate observed in the female family

control subjects under age 40(15). While the thyroid is known to increase in size during pregnancy, the occurrence of thyroid surgery soon after pregnancy is noteworthy(16). Thyroid hormone testing prior to and during pregnancy for those with thyroid disease or surgical hypothyroidism is recommended to enable optimizing thyroid hormone levels and is important for both maternal and fetal wellbeing (16, 29, 30).

Since risk of *DICER1*-associated tumors is a dominant trait, there is a 50% chance of transmitting the pathogenic allele to the fetus in each pregnancy regardless of whether the mother or the father harbors a pathogenic germline variant. Recently published surveillance guidelines suggest third-trimester ultrasound and chest x-ray at birth(31). As illustrated by one infant in this study, evidence of a cystic lung lesion on third trimester fetal ultrasound may enable subsequent postpartum diagnosis of *DICER1*-related pleuropulmonary blastoma. Suggested topics discussed with the family during genetic counseling during pregnancy include genetic testing of the child from cord blood or after birth for the parental *DICER1* variant, low penetrance for the most serious *DICER1*-associated phenotypes and initiation of surveillance guidelines for identification and treatment of malignancies which may improve outcomes(31, 32). Generally, if the child has a pathogenic *DICER1* variant, surveillance chest CT is recommended in infancy.

Routine gynecology care for *DICER1*-carriers includes individual and parent education regarding symptoms of abdominal or pelvic mass, changes in menstrual cycle or signs of virilization. Surveillance for either embryonal rhabdomyosarcoma or ovarian tumors may be best accomplished by gynecologic history and pelvic ultrasound every 6–12 months to facilitate early diagnosis and treatment(31). Clinical, laboratory (including AFP and male hormone testing) and ultrasound evaluation is recommended for female *DICER1*-carriers who present with virilization, amenorrhea or abdominal pain/distention or mass(1, 33). Particular vigilance using ultrasound and laboratory surveillance may be indicated for those using hormonal contraceptive methods that alter menstrual cycle events(31).

The strengths of this study include the thorough phenotyping of subjects, enrollment of a kindred of affected individuals enabling detailed medical histories and central pathology review. The limitations of this study include small numbers, incomplete data as life-long medical records could not be obtained and participation/ascertainment bias increasing the number of females with *DICER1*-related tumors, limiting the participation of those who may have milder phenotypes or those with more severe phenotypes who did not survive childhood. The number of infertile women may be limited as mothers of children with pleuropulmonary blastoma were enrolled.

Despite an elevated risk both of gynecologic tumors and other *DICER1*-related tumors, many women with *DICER1* pathogenic variants experience healthy reproductive lives. Importantly, we did not observe an increased risk of pubertal, menstrual or fertility issues among *DICER1* carriers. Surveillance and individual and family education for signs and symptoms of gynecologic tumors is warranted. The high rate of developing *DICER1*-related multinodular goiter was associated with high rates of thyroidectomy and underscores the importance of thyroid hormone monitoring and assessment in *DICER1*-carriers, especially during pregnancy.

Acknowledgments

Funding Source: This work was supported in part by the Intramural Research Program of National Institutes of Health, NIH Clinical Center, National Cancer Institute, National Human Genome Research Institute and National Institute for Neurological Disorders and Stroke. This study was presented in part at the American College of Obstetricians and Gynecologists 64th Annual Clinical and Scientific Meeting in Washington, DC from May 14–17, 2016.

REFERENCES:

1. Schultz KAP, Harris AK, Finch M, Dehner LP, Brown JB, Gershenson DM, et al. DICER1-related Sertoli-Leydig cell tumor and gynandroblastoma: Clinical and genetic findings from the International Ovarian and Testicular Stromal Tumor Registry. Gynecol Oncol 2017 12;147(3):521–7. [PubMed: 29037807]
2. Schultz KA, Harris A, Messinger Y, Sencer S, Baldinger S, Dehner LP, et al. Ovarian tumors related to intronic mutations in DICER1: a report from the international ovarian and testicular stromal tumor registry. Familial cancer 2016 1;15(1):105–10. [PubMed: 26289771]
3. Apellaniz-Ruiz M, de Kock L, Sabbaghian N, Guaraldi F, Ghizzoni L, Beccuti G, et al. Familial multinodular goiter and Sertoli-Leydig cell tumors associated with a large intragenic in-frame DICER1 deletion. Eur J Endocrinol 2018 2;178(2):K11–K9. [PubMed: 29187512]
4. Bahubeshi A, Bal N, Rio Frio T, Hamel N, Pouchet C, Yilmaz A, et al. Germline DICER1 mutations and familial cystic nephroma. J Med Genet 2010 12;47(12):863–6. [PubMed: 21036787]
5. Doros L, Schultz KA, Stewart DR, Bauer AJ, Williams G, Rossi CT, et al. DICER1-Related Disorders GeneReviews. 2014 4 24 ed Seattle (WA): University of Washington, Seattle; 1993–2018; 2014.
6. Fremerey J, Balzer S, Brozou T, Schaper J, Borkhardt A, Kuhlen M. Embryonal rhabdomyosarcoma in a patient with a heterozygous frameshift variant in the DICER1 gene and additional manifestations of the DICER1 syndrome. Familial cancer 2017 7;16(3):401–5. [PubMed: 27896549]
7. Hill DA, Ivanovich J, Priest JR, Gurnett CA, Dehner LP, Desruisseau D, et al. DICER1 mutations in familial pleuropulmonary blastoma. Science 2009 8 21;325(5943):965. [PubMed: 19556464]
8. Stewart DR, Messinger Y, Williams GM, Yang J, Field A, Schultz KA, et al. Nasal chondromesenchymal hamartomas arise secondary to germline and somatic mutations of DICER1 in the pleuropulmonary blastoma tumor predisposition disorder. Hum Genet 2014 11;133(11):1443–50. [PubMed: 25118636]
9. Rio Frio T, Bahubeshi A, Kanellopoulou C, Hamel N, Niedziela M, Sabbaghian N, et al. DICER1 mutations in familial multinodular goiter with and without ovarian Sertoli-Leydig cell tumors. JAMA 2011 1 5;305(1):68–77. [PubMed: 21205968]
10. Schultz KA, Pacheco MC, Yang J, Williams GM, Messinger Y, Hill DA, et al. Ovarian sex cord-stromal tumors, pleuropulmonary blastoma and DICER1 mutations: a report from the International Pleuropulmonary Blastoma Registry. Gynecol Oncol 2011 8;122(2):246–50. [PubMed: 21501861]
11. de Kock L, Sabbaghian N, Druker H, Weber E, Hamel N, Miller S, et al. Germ-line and somatic DICER1 mutations in pineoblastoma. Acta Neuropathol 2014 10;128(4):583–95. [PubMed: 25022261]
12. de Kock L, Sabbaghian N, Plourde F, Srivastava A, Weber E, Bouron-Dal Soglio D, et al. Pituitary blastoma: a pathognomonic feature of germ-line DICER1 mutations. Acta Neuropathol 2014 7;128(1):111–22. [PubMed: 24839956]
13. Stewart CJ, Charles A, Foulkes WD. Gynecologic Manifestations of the DICER1 Syndrome. Surg Pathol Clin 2016 Jun;9(2):227–41.
14. Khan NE, Bauer AJ, Doros L, Schultz KA, Decastro RM, Harney LA, et al. Macrocephaly associated with the DICER1 syndrome. Genet Med 2017 2;19(2):244–8. [PubMed: 27441995]
15. Khan NE, Bauer AJ, Schultz KAP, Doros L, Decastro RM, Ling A, et al. Quantification of Thyroid Cancer and Multinodular Goiter Risk in the DICER1 Syndrome: A Family-Based Cohort Study. J Clin Endocrinol Metab 2017 5 1;102(5):1614–22. [PubMed: 28323992]

16. American College of O, Gynecologists. Practice Bulletin No. 148: Thyroid disease in pregnancy. Obstet Gynecol 2015 4;125(4):996–1005. [PubMed: 25798985]
17. McDowell MA, Brody DJ, Hughes JP. Has age at menarche changed? Results from the National Health and Nutrition Examination Survey (NHANES) 1999–2004. J Adolesc Health 2007 3;40(3):227–31. [PubMed: 17321422]
18. Cabrera SM, Bright GM, Frane JW, Blethen SL, Lee PA. Age of thelarche and menarche in contemporary US females: a cross-sectional analysis. Journal of pediatric endocrinology & metabolism : JPEM 2014 1;27(1–2):47–51. [PubMed: 23959659]
19. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2013 12;98(12):4565–92. [PubMed: 24151290]
20. Schultz KA, Harris A, Williams GM, Baldinger S, Doros L, Valusek P, et al. Judicious DICER1 testing and surveillance imaging facilitates early diagnosis and cure of pleuropulmonary blastoma. Pediatr Blood Cancer 2014 9;61(9):1695–7. [PubMed: 24821309]
21. Gold EB. The timing of the age at which natural menopause occurs. Obstetrics and gynecology clinics of North America 2011 9;38(3):425–40. [PubMed: 21961711]
22. ACOG Practice Bulletin No. 200: Early Pregnancy Loss. Obstet Gynecol 2018 11;132(5):e197e207. [PubMed: 30157093]
23. Santoro N. Using Antimullerian Hormone to Predict Fertility. JAMA 2017 10 10;318(14):1333–4. [PubMed: 29049571]
24. Sklavos MM, Giri N, Stratton P, Alter BP, Pinto LA. Anti-Mullerian hormone deficiency in females with Fanconi anemia. J Clin Endocrinol Metab 2014 5;99(5):1608–14. [PubMed: 24438373]
25. Sklavos MM, Stratton P, Giri N, Alter BP, Savage SA, Pinto LA. Reduced serum levels of anti-Mullerian hormone in females with inherited bone marrow failure syndromes. J Clin Endocrinol Metab 2015 2;100(2):E197–203. [PubMed: 25405500]
26. Steiner AZ, Pritchard D, Stanczyk FZ, Kesner JS, Meadows JW, Herring AH, et al. Association Between Biomarkers of Ovarian Reserve and Infertility Among Older Women of Reproductive Age. JAMA 2017 10 10;318(14):1367–76. [PubMed: 29049585]
27. Elchuri SV, Patterson BC, Brown M, Bedient C, Record E, Wasilewski-Masker K, et al. Low Anti-Mullerian Hormone in Pediatric Cancer Survivors in the Early Years after Gonadotoxic Therapy. J Pediatr Adolesc Gynecol 2016 8;29(4):393–9. [PubMed: 26924632]
28. Johnson L, Sammel MD, Domchek S, Schanne A, Prewitt M, Gracia C. Antimullerian hormone levels are lower in BRCA2 mutation carriers. Fertil Steril 2017 5;107(5):1256–65 e6. [PubMed: 28476184]
29. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012 8;97(8):2543–65. [PubMed: 22869843]
30. Korevaar TI. Evidence-Based Tightrope Walking: The 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid 2017 3;27(3):309–11. [PubMed: 28257275]
31. Schultz KAP, Williams GM, Kamihara J, Stewart DR, Harris AK, Bauer AJ, et al. DICER1 and Associated Conditions: Identification of At-risk Individuals and Recommended Surveillance Strategies. Clinical cancer research : an official journal of the American Association for Cancer Research 2018 5 15;24(10):2251–61. [PubMed: 29343557]
32. Stewart DR, Best AF, Williams GM, Harney LA, Carr AG, Harris AK, et al. Neoplasm Risk Among Individuals With a Pathogenic Germline Variant in DICER1. J Clin Oncol 2019 3 10;37(8):668–76. [PubMed: 30715996]
33. Young RH, Perez-Atayde AR, Scully RE. Ovarian Sertoli-Leydig cell tumor with retiform and heterologous components. Report of a case with hepatocytic differentiation and elevated serum alpha-fetoprotein. Am J Surg Pathol 1984 9;8(9):709–18. [PubMed: 6206735]
34. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol 2018 2;131(2):e49–e64. [PubMed: 29370047]

35. Practice Bulletin No. 171: Management of Preterm Labor. Obstet Gynecol 2016 10;128(4):e155–64. [PubMed: 27661654]

36. Wallis AB, Saftlas AF, Hsia J, Atrash HK. Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987–2004. American journal of hypertension 2008 5;21(5):521–6. [PubMed: 18437143]

37. Knight M, Callaghan WM, Berg C, Alexander S, Bouvier-Colle MH, Ford JB, et al. Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group. BMC pregnancy and childbirth 2009 11 27;9:55. [PubMed: 19943928]

38. Locatelli A, Zagarella A, Toso L, Assi F, Ghidini A, Biffi A. Serial assessment of amniotic fluid index in uncomplicated term pregnancies: prognostic value of amniotic fluid reduction. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet 2004 4;15(4):233–6.

39. Tuuli MG, Norman SM, Odibo AO, Macones GA, Cahill AG. Perinatal outcomes in women with subchorionic hematoma: a systematic review and meta-analysis. Obstet Gynecol 2011 5;117(5):1205–12. [PubMed: 21508763]

40. Aloizos S, Seretis C, Liakos N, Aravosita P, Mystakelli C, Kanna E, et al. HELLP syndrome: understanding and management of a pregnancy-specific disease. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 2013 5;33(4):331–7. [PubMed: 23654309]

41. Gilstrap LC, 3rd, Ramin SM. Urinary tract infections during pregnancy. Obstetrics and gynecology clinics of North America 2001 9;28(3):581–91. [PubMed: 11512502]

42. Liu DB, Armstrong WR, 3rd, Maizels M. Hydronephrosis: prenatal and postnatal evaluation and management. Clinics in perinatology 2014 9;41(3):661–78. [PubMed: 25155734]

43. Ananth CV, Keyes KM, Hamilton A, Gissler M, Wu C, Liu S, et al. An international contrast of rates of placental abruption: an age-period-cohort analysis. PloS one 2015;10(5):e0125246. [PubMed: 26018653]

44. Lee SH, Lee JY, Choi YY, Lee JG. Laparoscopic appendectomy versus open appendectomy for suspected appendicitis during pregnancy: a systematic review and updated meta-analysis. BMC surgery 2019 4 25;19(1):41. [PubMed: 31023289]

45. London V, Grube S, Sherer DM, Abulafia O. Hyperemesis Gravidarum: A Review of Recent Literature. Pharmacology 2017;100(3–4):161–71. [PubMed: 28641304]

46. Sueyoshi M, Clevenger S, Hart E. Large Vaginal Varicosities in the Setting of Pregnancy without Known Hepatic or Vascular Risks: A Case Report and Review of the Literature. Case reports in obstetrics and gynecology 2018;2018:2394695. [PubMed: 29607234]

Highlights:

- Females with *DICER1*-related ovarian tumors frequently presented with virilization or amenorrhea.
- Those females with no history of ovarian tumors experienced normal pubertal development and regular menstrual cycles.
- Nearly all women who tried to conceive successfully delivered liveborn children.
- Reproductive-aged females underwent natural menopause at the same age as the general population.

Table 1:

Medical history of *DICER1*-carrier women with embryonal rhabdomyosarcoma

Patient	Age at Tumor (yrs)	Age at Menarche (yrs)	Pathology Report	Surgical Treatment	Chemotherapy
1: 141–1	7	14	Embryonal rhabdomyosarcoma uterine cervix, botryoid type	Trachelectomy	Yes
141–1	12	14	Embryonal rhabdomyosarcoma uterine cervix, botryoid type	Trachelectomy	Yes; also brachytherapy (36 Gy)
2: 193–1	11	13	Embryonal rhabdomyosarcoma cervix, botryoid type	Trachelectomy	Yes
3: 109–1	14	12	Embryonal rhabdomyosarcoma cervix, botryoid type	Trachelectomy, then hysterectomy	Yes

Table 2:

Medical history of *DICER1*-carrier women with Ovarian Sertoli Leydig cell tumors

Patient	Age at Menarche (yrs)	Age at Tumor (yrs)	Surgical Treatment	Pathology Report	Chemotherapy
1: 114–1	13	8	1st: Left oophorectomy, omentectomy	Sertoli-Leydig cell tumor, retiform variant	No
		14	2nd: Right salpingo-oophorectomy	Sertoli-Leydig cell tumor of intermediate differentiation	No
2: 151–1	14	13	Left salpingo-oophorectomy	Sertoli-Leydig cell tumor of intermediate differentiation	Yes
3: 145–4	11	14	1st: Right salpingo-oophorectomy	Unavailable, but mother said tumor had hair and teeth, suggesting dermoid cyst	No
		60	2nd: Left salpingo-oophorectomy	Sertoli-Leydig cell tumor of intermediate differentiation	Yes
4: 151–2	16	16	Left salpingo-oophorectomy	Unavailable, but menses resumed after oophorectomy	No
5: 135–1	11	16	Right salpingo-oophorectomy	Gynandroblastoma	No
6: 135–2	11	16	Right salpingo-oophorectomy	Gynandroblastoma	Yes
7: 168–1	13	17	Right oophorectomy	Sertoli-Leydig cell tumor of intermediate differentiation	No
8: 141–1	14	18	Right salpingo-oophorectomy	Sertoli-Leydig cell tumor of intermediate differentiation	No
9: 133–1	12	40	1st: Left salpingo-oophorectomy	Sertoli-Leydig cell tumor of intermediate differentiation	No
		40	2nd: Second surgery 3 months later; laparoscopic hysterectomy, Right salpingo-oophorectomy	Carcinoid tumor	No

Table 3:

Medical history of *DICER1*-carrier women with abnormal male hormone levels

Patient	Age (yrs)	Male Hormone Abnormality	Polycystic Ovarian Syndrome	Gynecology Clinical Details	*DICER1*-related Clinical details
1: 188–1	16	DHEA 691 ng/dL[1]	No	menarche age: 13 years regular menstrual cycles normal pelvic ultrasound no signs virilization Gravida 0	Status post treatment of pleuropulmonary blastoma type 1 at age 3 months
2: 104–1	17	DHEA 1289 ng/dL[1]	No	Menarche age: 14 years regular menstrual cycles normal pelvic ultrasound no signs virilization Gravida 0	Status post treatment of pleuropulmonary blastoma type III at 3 years and right frontal lobe brain metastasis from pleuropulmonary blastoma at age 6 years
3: 168–1	26	Androstenedione 219 ng/dL[2]	No	Menarche age: 13 years Regular menstrual cycles Normal pelvic ultrasound No signs virilization Gravida 0	Multinodular thyroid diagnosed at age 16 years, no intervention needed
4: 183–2	32	DHEA 645 ng/dL[1]; Androstenedione 201 ng/dL[2]	No	Menarche age: 11 years Status post hysterectomy for endometriosis Ultrasound: 6 mm echogenic lesion in right ovary No signs virilization Gravida 5 Para 3 spontaneous miscarriage 2	Papillary thyroid cancer, follicular variant age 13
5: 145–2	33	Androstenedione 271 ng/dL[2]	Yes	Menarche age: 13 years Regular menstrual cycles now but irregular as teen and diagnosis of PCOS then Ultrasound: normal No signs virilization Gravida 1 Para 1	Status post removal of cystic nephroma at age 1 year; thyroid nodules in early adulthood
6: 161–2	33	Androstenedione 431 ng/dL[3]	Yes	Menarche age: 11 years Irregular menstrual cycles due to PCOS Ultrasound: PCOS No signs virilization Gravida 3 Para 3	Thyroid cysts aspirated at age 14 and subtotal and complete thyroidectomies in early adulthood
7: 140–1	34	DHEA-S 4.1 mcg/mL[4]; DHEA 659 ng/dL[1]	Yes	Menarche age: unknown Irregular menstrual cycles treated with hormonal contraception Ultrasound: not done No signs virilization Gravida 3 Para 2 spontaneous miscarriage 1	Status post pleuropulmonary blastoma type 1 at age 2; benign thyroid nodules with partial and complete thyroidectomies in adolescence
8: 140–2	37	Androstenedione 237 ng/dL[2]; 17-OHP 182 ng/dL[5]	Yes	menarche age: 14 years Menstrual cycles regular until last 6 months then menses every 2–3 months. Ultrasound: PCOS Virilization: acne and hirsutism Gravida 4 Para 3 spontaneous miscarriage 1	Recurrent multinodular goiter status post total thyroidectomy at age 15 years
9: 129–2	40	17-OHP 398 ng/dL[5]	No	Menarche age: 12 years Regular menstrual cycles Normal pelvic ultrasound No signs virilization Gravida 2 Para 1 spontaneous miscarriage 1	Multinodular thyroid at age 36, no intervention

[1] DHEA reference range: 0–599 ng/dL

[2] Androstenedione reference range: 17–175 ng/dL

[3] Androstenedione reference range: 30–200 ng/dL

[4] DHEA-S reference range: .35–4.30 mcg/mL

[5] 17-OHP reference range: 3–175 ng/dL

Table 4:

Pregnancy complications

	Total Pregnancies n=83	Total Women with Completed Pregnancies n=32	Pregnancy Rates in the General Population (%)
Complication	**# pregnancies (%)**	**# mothers (%)**	
Gestational diabetes	6 (7.2%)	4 (12.5%)	6(34)
Preterm labor	5 (6.0%)	4 (12.5%)	12(35)
Gestational hypertension	5 (6.0%)	3 (9.4%)	21.3(36)
Postpartum hemorrhage	2 (2.4%)	2 (6.3%)	3–5(37)
Oligohydramnios	2 (2.4%)	1 (3.1%)	11(38)
Subchorionic hemorrhage	2 (2.4%)	1 (3.1%)	0.5–22(39)
Severe Preeclampsia/HELLP	1 (1.2%)	1 (3.1%)	0.9(40)
Pyelonephritis	1 (1.2%)	1 (3.1%)	1–2(41)
Bilateral hydronephrosis	1 (1.2%)	1 (3.1%)	1–4.5(42)
Placental abruption	1 (1.2%)	1 (3.1%)	7–12(43)
Appendectomy	1 (1.2%)	1 (3.1%)	.18–4.1(44)
Hyperemesis Gravidarum	1 (1.2%)	1 (3.1%)	.3–3.0(45)
Vulvar varicosities	1 (1.2%)	1 (3.1%)	2–4(46)