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Gynecologic and Reproductive Health of Women with Telomere Biology Disorders

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Summary

Reproductive health may be adversely impacted in women with dyskeratosis congenita (DC) and related telomere biology disorders (TBD). We evaluated gynecologic problems, fertility, and pregnancy outcomes in 39 females aged 10 to 81 years followed longitudinally in our DC/TBD cohort. Twenty-six had bone marrow failure and 12 underwent hematopoietic cell transplantation. All attained menarche at a normal age. Thirteen women reported menorrhagia; ten used hormonal contraception to reduce bleeding. Nine experienced natural normal-aged menopause. Gynecologic problems (endometriosis=3, pelvic varicosities=1, cervical intraepithelial neoplasia=1 and uterine prolapse=2) resulted in surgical menopause in seven. Twenty-five of 26 women attempting fertility carried 80 pregnancies with 49 (61%) resulting in livebirths. Ten (38%) women experienced 28 (35%) miscarriages, notably recurrent pregnancy loss in five (19%). Preeclampsia (n=6, 24%) and progressive cytopenias (n=10, 40%) resulted in maternal-fetal compromise, including preterm (n=5) and cesarean deliveries (n=18, 37%). Gynecologic/reproductive problems were noted mainly in women with autosomal-dominant inheritance; others were still young or died early. Although women with TBDs had normal menarche, fertility, and menopause, gynecologic problems and pregnancy complications leading to cesarean section, preterm delivery, or transfusion support were frequent. Women with TBDs will benefit from multidisciplinary, coordinated care by hematology, gynecology and maternal-fetal medicine.

Keywords

Dyskeratosis congenita; telomere biology disorder; reproductive health; pregnancy loss; pregnancy complications

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Introduction

Dyskeratosis congenita (DC) and related telomere biology disorders (TBD) are inherited bone marrow failure syndromes (IBMFS) with broad phenotypic spectrums and complex clinical manifestations(Niewisch and Savage 2019). Classical DC has the triad of dysplastic nails, abnormal skin pigmentation, and oral leukoplakia. Patients also have high rates of bone marrow failure (BMF), head and neck squamous cell carcinoma (SCC), myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), pulmonary fibrosis, and liver disease and other medical complications(Alter, *et al* 2018, Niewisch and Savage 2019). Telomere lengths below the first percentile for age are diagnostic and are due to pathogenic germline variants in more than 14 telomere biology genes with autosomal dominant (AD), autosomal recessive (AR), or X-linked recessive (XLR) inheritance, or *de novo* occurrence. Patients with AR, XLR inheritance or AD *de novo TINF2* variants generally have exceedingly short telomeres, multisystem disease, and earlier age at symptoms than AD non-*TINF2* DC/TBD(Alter, *et al* 2012, Bhala, *et al* 2019, Giri, *et al* 2019, Ward, *et al* 2018). The term TBD encompasses the clinical manifestations and multimodal inheritance of this complex spectrum of disease due to aberrant telomere biology.

Telomeres, nucleoprotein complexes at chromosome ends, are essential for genomic stability and shorten with each cell division (de Lange 2010). Telomere shortening in gonadal tissue occurs during normal aging, associated with premature ovarian failure and subfertility in the general population(Keefe 2016). Anti-Mullerian hormone, a marker of reduced ovarian reserve, is low in women with DC and other IBMFS(Sklavos, *et al* 2014, Sklavos, *et al* 2015).

Women with IBMFS, including DC/TBD, may develop worsening cytopenias during pregnancy, requiring transfusions; these cytopenias could contribute to adverse maternal and fetal outcomes(Alter, *et al* 1999, Gansner, *et al* 2017, Giri, *et al* 2017). Reduced fertility and increased fetal and maternal complications were reported during pregnancy in women with Fanconi anemia, Diamond Blackfan anemia and Shwachman Diamond syndrome(Alter, *et al* 1991, Faivre, *et al* 2006, Nabhan, *et al* 2010, Sorbi, *et al* 2017). Reports on reproductive health and pregnancy outcomes in women with DC/TBD are limited(Gansner, *et al* 2017, Giri, *et al* 2017).

Here we describe gynecologic and reproductive health in a cohort of women with DC/TBD and examine associations with the mode of inheritance.

Methods

We evaluated females with DC/TBD aged 10 years or older enrolled in the National Cancer Institute's IBMFS cohort study (ClinicalTrials.gov identifier NCT00027274) between 2002 and June 30, 2019(Alter, *et al* 2018). All study participants or their legal guardian signed informed consent. DC was diagnosed due to the mucocutaneous triad and/or other DC-related clinical features and telomeres <1st percentile for age in peripheral blood lymphocytes(Alter, *et al* 2012, Vulliamy, *et al* 2006). Individuals with mucocutaneus triad features and BMF comprised "classic DC" and included subtypes such as Hoyeraal-

Hreidarsson syndrome (HH) when associated with cerebellar hypoplasia, or Coats plus with cerebroretinal microangiopathy(Niewisch and Savage 2019). BMF was defined by cytopenias with blood counts below standard reference ranges for age and gender(Brugnara 2009). Severe BMF was classified as hemoglobin less than 80 g/L, absolute neutrophils less than 0.5×10^9/L, and platelets less than 30×10^9/L, or on treatment or having received hematopoietic cell transplantation (HCT) for BMF; values below normal for age but not severe were included as non-severe BMF(Alter, *et al* 2007). Individuals with no triad features or BMF who had very short telomeres and findings suggestive of TBD such as pulmonary fibrosis, head and neck SCC, or chronic enteropathy, were considered "DC-like". The diagnosis of DC/TBD was confirmed by identification of pathogenic variants in known DC-associated genes. Asymptomatic female relatives with very short telomeres and the proband's pathogenic variant in DC/TBD genes were included as affected individuals and called "silent carriers".

Detailed clinical information on the participants was obtained from review of study-related forms and medical records, and 20 (51%) of women were evaluated at the National Institute of Health Clinical Center by the study gynecologist (P.S.). We determined gynecological history, age at menarche and menopause, details regarding fertility, pregnancy, and maternal and fetal outcomes of pregnancy. We ascertained the impact of hematologic abnormalities on menstrual flow and pregnancy outcomes such as need for transfusion support and preterm birth.

Statistical analyses were performed using Microsoft Excel Office 365 (Microsoft, Redmond, WA) and Stata 16.1 software (StataCorp, College Station, TX). P values <0.05 were significant. Characteristics of patients with AD non-*TINF2* DC/TBD were compared with patients with AR, XLR, AD or *de novo TINF2* and DC with unknown gene variant by Kruskal-Wallis for continuous variables and Fisher's exact for categorical variables. AD non-*TINF2* DC patient data were compared with all other groups combined due to differences in disease manifestations, severity and age at diagnosis(Alter, *et al* 2012, Bertuch 2016, Ward, *et al* 2018).

Results

Participant demographics

Thirty-nine women ranging in age from 10–81 years (median 33 years) with DC/TBD were evaluated. Twenty-six women (67%) had BMF identified at a median age of 18 years (range 2–46); eight had non-severe and 18 had severe BMF. Six women with severe BMF received androgens for cytopenias; four long-term (2–15 years); two stopped after a year due to lack of sustained hematological response. No one took androgens around the time they became pregnant. Twelve women underwent HCT at a median age of 25 years (range 9–63) for severe aplastic anemia (n=10) or AML (n=2). Five women had no cytopenia but had some features suggestive of DC (DC-like) and eight asymptomatic women had pathogenic variants in DC/TBD genes identified through family testing (silent carriers, Table I).

Inheritance was AD (non-*TINF2*) in 26, AD-*TINF2* in three (1 *de novo*), AR in four, and unknown in six (Table II). Women with AD (non-*TINF2*) DC were significantly older at

diagnosis (p=0.0005), at study (p=0.0005), and at last follow-up (p=0.0003) than those with AD-*TINF2*, AR or unknown gene (Table II). They were also more likely to be designated as DC-like (n=4) or had no features (n=8) of DC (p=0.034), developed BMF at an older age (p=0.004), and were less likely to have received HCT (p=0.002) than women with AD-*TINF2*, AR or unknown gene. AD (non-*TINF2*) women were also more likely to reach adulthood and plan pregnancy (p=0.002). Women with AD-*TINF2*, AR or unknown inheritance were more likely to have multisystem manifestations at a younger age that needed medical care and were less likely to have reached adulthood at last follow-up; two had HH and two had Coats plus.

Reproductive and gynecologic history

All 39 women attained menarche at normal ages (median 12 years; range 9–17). Detailed menstrual history was available for 30 women; 13 of these women reported heavy periods. In nine women, the heavy periods could be attributed to underlying cytopenia; seven had severe pancytopenia with platelets below 20×10^9/L and two with non-severe cytopenia had platelets in 60–90×10^9/L range. Three of four women with no cytopenia had endometriosis as a contributing factor. Nineteen used hormonal contraception, generally to prevent pregnancy, but 10 reported this also decreased menstrual bleeding.

Nine women had natural menopause at a median age of 49 years (range 46–52). The age at menopause was indeterminate for one who developed amenorrhea at age 46 while taking androgen for cytopenia. Seven women (44%) experienced surgical menopause following hysterectomy with oophorectomy for endometriosis (n=3, age 28, 30, 30 years), pelvic varicosities associated with pelvic fluid and pain independent of ovulation (n=1, age 33 years) with resolution of symptoms after hysterectomy, cervical intraepithelial neoplasia (CIN 3) (n=1, age 37 years) and uterine prolapse, one with and one without CIN 3 (n=2, age 51, 54 years) (Table III). Twelve of 32 sexually active women reported a history of anogenital HPV infection and six required treatment. Four participants developed tongue SCC (age 14, 27, 42, and 48 years), two had skin SCC (age 16 and 35 years); none developed gynecologic cancer during the study period.

Fertility and Pregnancy

Twenty-six women ≥16 years of age who attempted pregnancy carried 80 pregnancies; 25 gave birth to at least one liveborn child (median age at 1st pregnancy 25 years, range 16–38 years, Table III). Six of these (23%) sought evaluation for infertility that was subsequently attributed to endometriosis (n=1), scarred/blocked fallopian tubes (n=3), or anovulation (n=2). These six women received follicle stimulating agents or underwent *in vitro* fertilization or intrauterine insemination.

Forty-nine of 80 pregnancies (61%) in 25 women resulted in 51 livebirths including two sets of twins. In contrast, 28 pregnancies (35%) in 10 women (40%) ended in miscarriage or mid-trimester losses at rates significantly higher than the expected general population rate of 10–20% (p=0.02-<0.0001)(Regan and Rai 2000, Stirrat 1990). Three women terminated one pregnancy each. Five women (20%) had recurrent first trimester miscarriages (≥2 at <12 weeks gestation), a significantly higher rate than the expected general population rate

of 1–3% (p=0.008-<0.0001)(Jeve and Davies 2014). Two women each experienced two mid-trimester pregnancy losses at 19–20 weeks (Table III).

Eight of the 49 pregnancies (16%) resulting in livebirths were delivered preterm (≤36 weeks) and occurred in seven women (Table III). Five had preeclampsia, which was severe in four [including hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome], one had excessive bleeding during delivery at 32 weeks and two were cesarean sections at 36 weeks. In all, six of 25 women (24%) experienced preeclampsia in six of 49 pregnancies (12%) that was severe in most compared with the general population rate of 2–8% (p = 0.01–0.39) (ACOG 2019, Bateman, *et al* 2012). Thirty-seven percent (18/49) of all livebirths were C-section deliveries for maternal and/or fetal complications with 44% (11/25) of women undergoing at least one (primary) C-section. The preterm birth rate of 16% was similar to the population rate of 9.5% (p=0.27); however, the primary cesarean delivery rate (44% versus 18.5%; p=0.001) was significantly higher than the general US population(Ananth, *et al* 2017, Ferre, *et al* 2016). Two women had gestational diabetes in their early 30s.

Hematological abnormalities during pregnancy or delivery such as clinically significant declining platelet counts or hemoglobin (n=7), or severe post-partum hemorrhage resulting in low hemoglobin (n=5), occurred in 12 pregnancies (24%) among 10 of 25 women (40%) (Table III). Seven of these 10 women had hematologic symptoms prior to pregnancy, but only three of the seven had been diagnosed with DC/TBD before pregnancy. Placenta previa with abruption occurred in two pregnancies in one of these 10 women; she used a pregnancy surrogate for her next child. Overall, seven women required platelet and/or red blood cell transfusions and two were treated for hemorrhage with a dilatation and curettage (one after delivery and one after delayed post-abortion hemorrhage). Blood counts improved to pre-pregnancy levels within 6–12 weeks after delivery in all but two women who had severe BMF before pregnancy.

Pregnancy and hematopoietic stem cell transplantation

Only one of the 26 women with pregnancy had undergone HCT prior to childbearing. She had two pregnancies beginning at 6 years after HCT; one using a donor egg and one with *in vitro* fertilization and preimplantation genetic diagnosis to exclude an affected embryo. Three of 12 women who underwent HCT had completed their childbearing prior to HCT. Two women undertook fertility preservation by oocyte cryopreservation in their twenties prior to HCT. One of these two has not yet attempted pregnancy. The other had a low AMH (0.3ng/ml) and poor yield following ovarian stimulation; she died from complications of HCT. Three of the six other women who received HCT died at ages 16, 24 and 28 years and three are alive at ages 18, 18 and 25 years (two after also receiving liver transplant).

Reproductive health and DC/TBD inheritance

We explored whether there were associations between female reproductive health and mode of inheritance of DC/TBDs. Twenty-two of 25 parous women had AD non-*TINF2* inheritance, two had *TINF2* and one was unknown (Table III). In contrast, four of 14 nulliparous women had AD non-*TINF2* inheritance while 10 had AR (n=4), de novo *TINF2* (n=1) or unknown gene variant (n=5) (p<0.0001). Eight parous women with AD DC/TBD

were asymptomatic (silent carriers) and five others had no hematologic manifestations. Twelve had BMF (severe=8, non-severe=4), seven developed BMF before pregnancy and five later in life (median age at BMF 29 years, range 2–46). In contrast, 13 of 14 nulliparous women had BMF (p=0.001) at a median age of 14 years, range 3–32 (p=0.004). BMF was severe in 11 and seven received HCT (median age 18 years, range 9–28). The parous women were older at last follow-up (median age 47 years, range 17–81) and seven are deceased (median age 57 years, range 44–63) compared with the nulliparous women who were younger (median age at last follow-up 22 years, range 12–39; p=0.0001) and four are deceased (median age 26 years, range 16–31; p=0.0002). Two older nulliparous women (age 35 and 39 years) with AD inheritance had not considered pregnancy due to disease-related morbidity while the eight others are still young (median age 18.5 years, range 12–28).

Discussion

This study found that women with DC/TBDs attained menarche at normal age. Notably, the women with DC/TBD due to AD inheritance underwent natural menopause at normal ages and the rate of surgical menopause was similar to the general population(Wang, *et al* 2013). Despite low AMH levels suggestive of low ovarian reserve in our prior study of 15 women with DC(Sklavos, *et al* 2015), women in the current study were fertile, although they had lower fecundability and some needed fertility assistance. Some women used assisted reproduction to avoid hematologic complications during pregnancy, to avoid delivering an affected fetus, or for fertility preservation prior to HCT. However, one woman with low AMH had a poor ovarian response to controlled ovarian stimulation, while experiencing a transient increase in leukocyte telomere length(Robinson, *et al* 2020). This finding could be related to the estrogen response element within the TERT promoter(Calado, *et al* 2009). Scarred fallopian tubes noted in three of six infertile women with DC was also reported by others(Gansner, *et al* 2017). It is unclear whether this is a manifestation of DC akin to stenosis of lacrimal duct, esophagus, or urethra or secondary to other causes like prior infection(Niewisch and Savage 2019).

The recurrent miscarriage rates in women with DC were higher than in the general population(Jeve and Davies 2014) and occurred at younger ages than expected. The occurrence of recurrent mid-trimester losses in two women without hematologic disease or other known causes like cervical incompetence, and of recurrent placenta previa in one woman is also noteworthy. While the preterm birth rate was similar, the primary cesarean delivery was significantly higher than in the general US population(Ananth, *et al* 2017).

More pregnancies were complicated by preeclampsia, especially severe preeclampsia, in comparison with the general population(ACOG 2019, Bateman, *et al* 2012), which was the primary cause of preterm birth and fetal intrauterine growth restriction (IUGR). Preeclampsia was associated with worsening cytopenias during pregnancy. Although the risk of preeclampsia is generally lower in the second pregnancy, two women reported preeclampsia in the second rather than first pregnancy. The higher rates of preeclampsia are similar to those previously reported in DC and another IBMFS, Fanconi anemia(Alter, *et al* 1991, Giri, *et al* 2017).

The occurrence of acquired aplastic anemia during pregnancy has been shown to result in fetal and maternal complications including IUGR, preterm birth and neonatal death and preeclampsia and other adverse outcomes in mothers(Deka, *et al* 2003, Tichelli, *et al* 2002). Monitoring of hematologic parameters and maternal transfusion support has improved both maternal and fetal outcomes(Killick, *et al* 2016, Kwon, *et al* 2006). A few women in our study who developed hematologic complications during pregnancy had cytopenias prior to pregnancy while others developed cytopenia during pregnancy. There were no pregnancy-associated maternal deaths related to cytopenia or otherwise.

Heavy periods associated with cytopenias treated with hormonal contraceptives occurred commonly, potentially representing a gynecologic feature of hematologic complications associated with DC. Overall, endometriosis accompanied by heavy, painful menses occurred in 16% of fertile women similar to the general population prevalence of 10%(Zondervan, *et al* 2020). The women who underwent hysterectomy for endometriosis had each successfully delivered a liveborn child despite experiencing recurrent pregnancy loss. While heavy, painful menses are common among women with endometriosis, having pain meriting hysterectomy by age 30 and experiencing recurrent pregnancy loss is uncommon. The occurrence of recurrent nonmalignant pelvic fluid that abated after hysterectomy and salpingo-oophorectomy is also noteworthy.

Impairment of telomerase homeostasis in the placentas of women without DC/TBD has been reported in cases with recurrent miscarriages, stillbirth, and abruption(Hapangama, *et al* 2017, Sõber, *et al* 2016, Sultana, *et al* 2018, Workalemahu, *et al* 2016). Differential regulation of placental telomerase activity and telomere length occurs over pregnancy and is not understood. Placental ageing is induced by telomere shortening and both have been observed in preeclampsia and IUGR(Biron-Shental, *et al* 2016, Biron-Shental, *et al* 2010, Rana, *et al* 2019, Sultana, *et al* 2018). Telomerase activity shows dynamic changes in human endometrium correlating with the ovarian cycle (mirroring its dynamic steroid production) and with glandular proliferation, likely playing a role in both the occurrence of heavy menses and development of endometriosis(Hapangama, *et al* 2017). Thus, pregnancy losses, placenta previa, preeclampsia, heavy menses, and endometriosis risk in our cohort of DC/TBD are likely due to impaired telomere homeostasis in mothers and/or their placentas and are worthy of further studies. Despite these adverse reproductive events, aberrant germline telomere biology did not appear to result in early reproductive aging as women with AD inheritance generally underwent natural menopause at normal ages.

The relatively normal reproductive health of women with DC/TBDs with AD inheritance contrasts with impaired reproductive health in women with other IBMFS(Alter, *et al* 1991, Alter, *et al* 1999). Women with Fanconi anemia generally experience primary ovarian insufficiency by age 30 evidenced by an extremely low AMH level, infertility, and early menopause(Giri, *et al* 2007, Petryk, *et al* 2015, Sklavos, *et al* 2014). DC women with more severe disease manifestations at young ages merited specialized care that took priority over reproductive concerns hampering assessment of their potential ovarian insufficiency and fertility.

Our study was limited by lack of in person evaluation of nearly 50% of women and reliance on data abstraction from medical records. The strengths of our study are the systematically collected information in a large cohort of patients and evaluation by the same gynecologist for those seen in clinic. Study staff received essentially real-time notification about new or worsening obstetric and gynecologic complications.

Women with DC/TBD with AD inheritance generally experienced a normal reproductive life in which they attained menarche, were fertile despite reduced fecundability, and underwent natural menopause at normal ages. Women with AD DC/TBD may live up to their fifth or sixth decade(Alter, *et al* 2018). Despite the increased risk of cancer, they do not appear to be at increased risk of gynecologic malignancy. Endometriosis, heavy menses, and recurrent pregnancy loss may complicate their reproductive life. Assisted reproductive technologies aided the few who were infertile and enabled family-building, underscoring the importance of considering oocyte or embryo cryopreservation independent of HCT in women with TBDs. However, as illustrated in a DC case report (Robinson, *et al* 2020), assisted reproductive techniques do not ensure fertility nor will they protect against miscarriage. Importantly, TBDs remain lethal diseases in many women illustrating the importance of discussing posthumous disposition of cryopreserved oocytes and embryos as part of shared decision-making regarding fertility preservation. A high proportion of women with DC/TBD appear to have complications during pregnancy associated with preeclampsia and worsening cytopenia needing transfusion support. These complications may lead to increased likelihood of cesarean and preterm delivery. These observations illustrate that all pregnancies in women with DC/TDB benefit from coordinated care by hematologists with expertise in IBMFS and maternal-fetal medicine specialists.

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Table I:

Description of the Cohort

DC/TBD Classification	N 39	Age at Study Years (range)	Major Manifestation		Affected Genes*
			Hematologic	Non-hematologic	
Classic DC	22	31 (13–63)	22	1 GI	10 *TERC*, 3 *TINF2*, 4 *TERT*, 1 *CTC1*, 4 gene unknown
Hoyeraal-Hreidarsson	2	10, 18	2		2 *RTEL1* (AR)
Coats plus	2	17, 31	2		1 *CTC1*, 1 gene unknown
DC-like	5	32 (17–50)	mild anemia 1	2 tongue HNSCC, 2 GI + other non-specific symptoms, 1 pulmonary fibrosis	1 *TERC*, 1 *TERT*, 1 *RTEL1* (AD), 1 *MDM4*, 1 gene unknown
Silent carrier	8	51 (30–81)	none	none	1 *TERC*, 4 *TERT*, 3 *RTEL1* (AD)

DC = dyskeratosis congenita; TBD = telomere biology disorder; HNSCC = head and neck squamous cell carcinoma; GI = gastrointestinal; AR = autosomal recessive; AD = autosomal dominant.

Classic DC = 2 or more features of mucocutaneous triad ± other manifestations (Vulliamy and Dokal 2006); Hoyeraal-Hreidarsson and Coats plus are included as subtypes of Classic DC. DC-like = individuals with lymphocyte telomeres <1st percentile by flow cytometry with *in situ* hybridization and lacking mucocutaneous triad and bone marrow failure. Silent carriers = asymptomatic family members with very short telomeres and pathogenic variants in DC/TBD genes.

* pathogenic variants in *TINF2, TERC* and *TERT* were AD, *CTC1* AR, and *RTEL1* AD or AR.

Table II:

Inheritance patterns of study participants

	AD (non-*TINF2*)	AD-*TINF2*	AR	Unknown	P value
Number	26	3	4	6	
Genes	12 *TERC*, 9 *TERT*, 4 *RTEL1*, 1 *MDM4*	1 *de novo*, 2 inherited	2 *RTEL1* 2 *CTC1*		
Age at DC/TBD diagnosis, y	42 (15–81)	4, 10, 33	15 (9–16)	15 (11–29)	0.0005
Age at study, y Median (range)	46 (16–81)	13, 27, 47	17 (14–18)	18 (13–31)	0.0005
BMF, N (%)	15 (58%)	3 (100%)	4 (100%)	5 (96%)	0.151
Age at BMF, y	27 (14–46)	3, 10, 33	14 (6–16)	8 (2–21)	0.0043
HCT, N (%)	4 (15%)	3 (100%)	3 (75%)	2 (33%)	0.002
Pregnancy, N (%)	22 (85%)	2 (67%)	0	2 * (33%)	0.002
Age at 1st pregnancy, y	27 (17–38)	21, 31		16, 17	0.03
Age at LFU or death, y	46 (25–81)	16, 40, 47	18 (17–26)	18 (13–32)	0.0003
N died	7	2	0	2	0.277
Age at death, y	57 (25–63)	16, 47		29, 32	0.23

AD = autosomal dominant; AR = Autosomal recessive; UK = unknown; LFU = last follow-up; BMF = bone marrow failure; N = number; HCT = hematopoietic cell transplant

* 1 induced abortion at age 17 years; y = years. All ages are median (range)

All P values are global comparing AD non-*TINF2* DC, *TINF2*, AR and unknown using Pearson chi^2 for categorical and Kruskal-Wallis for continuous variables (Stata/SE 16.1 version). All P values were more significant when AD non-*TINF2* DC was compared with all others as one group (*TINF2*, AR and unknown) which were similar to each other (data not shown).

Table III:

Pregnancy Complications, Obstetric and Gynecologic History of Women with DC/TBDs

UPN	Gravida	Fetal outcomes		Maternal complications during pregnancy			Other obstetric and gynecologic conditions	Affected gene (inheritance)	Pathogenic variant
		Fetal losses ≤ 20 wks	Live birth > 20 wks	Hematologic		Obstetric includes c-section and forceps			
				Baseline	During pregnancy				
6–1	3	1 miscarriage	2 term	normal	platelets ↓↓↓, Tx	placenta previa + abruption x 2; C-sections	1 baby through surrogate mother, VIN 1 excised age 51	*TERC* (AD)	n.97_98delCT
6–3	2	none	2 normal term	normal	normal	none	hysterectomy age 37 for CIN 3	*TERC* (AD)	n.97_98delCT
26–3	1	none	preterm twins-33 weeks	SAA	↓↓↓ SAA, Tx	preeclampsia; C-section	none	*TERT* (AD)	
74–1	2	none	2 normal term	normal post-BMT	normal	none	IVF; 1 for donor egg; 1 for PGD	*TINF2* (AD)	c.838A>G
114–1	3	1 miscarriage; 1 ectopic	1 preterm at 32 weeks	↓ platelet	↓↓↓ Hb & platelets, severe bleeding, Tx	precipitous preterm labor	Scarred fallopian tubes; difficulty getting pregnant; D and C for heavy bleeding	*TERC* (AD)	n.100T>A
114–3	2	1 miscarriage	1 term	↓ platelet	↓↓↓ SAA, severe bleeding; Tx	C-section for SAA	none	*TERC* (AD)	n.100T>A
164–3 *	2	none	1 fetal distress; 1 IUGR, both at term	normal	normal	C section x 2 for fetal indications	none	*RTEL1* (AD)	c.2956C>T
164–4 *	4	none	4 term	normal	normal	none	none	*RTEL1 (*AD)	c.2956C>T
196–2	2	none	1 term died day 1, 1 term	macrocytosis	macrocytosis	preeclampsia with 2nd pregnancy	none	*TINF2 (*AD)	c.873G>C,
201–1	1	none	1 normal term	↓ platelet	↓ platelet	none	none	unknown	
220–2 *	6	2 miscarriages	3 term; 1 preterm-36 weeks	normal	normal	C-section x 4: all failure to progress	hysterectomy age 30 for endometriosis; ovarian vein thrombosis, age 31; poor wound healing after surgery	*TERT (*AD)	c.2110C>T
226–8	4	2 mid-trimester losses	1 preterm-27 weeks; 1 term	normal	normal	C-section: preeclampsia, IUGR; gestational diabetes	Infertility; took fertility drugs for pregnancy	*MDM4* (AD)	c.1361C>T

UPN	Gravida	Fetal outcomes		Maternal complications during pregnancy			Other obstetric and gynecologic conditions	Affected gene (inheritance)	Pathogenic variant
		Fetal losses ≤ 20 wks	Live birth > 20 wks	Hematologic		Obstetric includes c-section and forceps			
				Baseline	During pregnancy				
238–2	6	3 miscarriages; 1 abortion	2 term	normal	normal	heavy bleeding 5 weeks after abortion	hysterectomy age 28 for endometriosis	*RTEL1* (AD)	c.1861G>A
327–3	2	none	1 term; 1 twins term	↓ counts	↓↓ Hb & platelets	none	none	*TERC* (AD)	n.334_339dupGGGGCG
327–2*	2	none	1 term; 1 preterm-36 weeks	normal	normal	C-section x 2: 1 failure to progress; 1 preeclampsia	hysterectomy age 33 for pelvic varicosities	*TERC* (AD)	n.334_339dupGGGGCG
350–1	2	none	2 term	macrocytosis	macrocytosis	1 forceps	hysterectomy age 51 for prolapsed uterus	*TERC* (AD)	n.114_115delTT
353–1	3	2 miscarriages	1 fetal distress term	normal	normal	C-section for fetal distress	endometriosis; infertility; many IVF attempts; LEEP for CIN II, age 32	*TERT* (AD)	
350–3	1	none	1 preterm 33 weeks	↓ platelet	HELLP, ↓↓↓ Hb & platelets, Tx	c-section for severe preeclampsia	IVF for PGD	*TERC* (AD)	n.114_115delTT
556–1*	2	none	2 term	normal	↓ platelet	gestational diabetes	none	*TERT* (AD)	c.1156_1171del,
543–2*	2	none	2 term	normal	Low counts after post-partum hemorrhage	1 post-partum hemorrhage; 1 elective C-section	none	*TERT* (AD)	c.2591T>C
520–1	2	none	2 term	normal	normal	2 forceps	none	*TERC* (AD)	n.234C>G
545–2	2	none	2 preterm, 1– 28 weeks, 1– 36 weeks	↓ counts	↓↓ Hb & platelets	c-section at 28 weeks for preeclampsia; c-section at 36 weeks	took fertility hormones to conceive	*TERT* (AD)	c.3205G>A
522–2	5	3 miscarriages	2 term	none	none	1 vanishing twin	PCOS, scarred fallopian tubes, took fertility drugs for pregnancy; hysterectomy age 54 for prolapse	*TERT* (AD)	c.2768C>T
449–2*	13	10 miscarriages; 2 mid-trimester losses	1 term	none	none	recurrent pregnancy losses	hysterectomy age 30 for endometriosis	*TERT* (AD)	c.2947C>T
518–2*	4	none	4 term	none	none	none	none	*RTEL1* (AD)	

Abbreviations: CIN = cervical intraepithelial neoplasia; C-section = cesarean section; D and C = dilation and curettage; HELLP = hemolysis elevated liver function tests low platelets (severe preeclampsia) IVF = in vitro fertilization; IUGR = intrauterine growth restriction; LEEP = loop electrocautery excision procedure; PGD = preimplantation genetic diagnosis; PCOS = polycystic ovarian syndrome; Tx = transfusions.

↓ = mild cytopenia

↓↓ = moderate cytopenia

↓↓↓ = severe cytopenia needing transfusions. UPN = unique patient number. VIN = vulvar intraepithelial neoplasia

* Silent carriers: No DC-associated features, identified by mutation testing after the diagnosis of an affected offspring.

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