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Letter to Blood

TO THE EDITOR:

Diminished ovarian reserve in young women with sickle cell anemia

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Information about whether sickle cell anemia (SCA) and its treatments affect female fertility is needed.[1] Diminished ovarian reserve (DOR) describes low egg supply, is considered irreversible in women with cancer,[2] and is a risk factor for recurrent pregnancy loss,[3] miscarriage,[4] and infertility.[5] Women with SCA (>30 years old) have higher rates of DOR than age-matched controls.[6-8] In a study of 10- to 21-year-old females with SCA, DOR occurred in 24% (8 of 33) of the hydroxyurea-treated subjects and none of the 14 untreated subjects.[9] In cancer, DOR before chemotherapy is a risk factor for posttreatment infertility[10] and an indication for fertility preservation.[11] Fertility preservation for pre- and postpubescent females[12,13] before gonadotoxic treatment is a care standard and offered to individuals with SCA before curative therapies.[14,15] Fertility care may be more broadly indicated for people with ovaries and SCA.

In postpubescent individuals, ovarian reserve is measured using antimullerian hormone (AMH), a biomarker of the ovarian follicle pool, follicle-stimulating hormone (FSH), and antral follicle count (AFC).[16] These tests, originally used for infertility assessments, now inform fertility preservation decisions.[11] Complete ovarian reserve tests in SCA are not reported. This study's primary objective was to measure ovarian reserve in women under 31 years old with SCA, compare measures in age-stratified subgroups, and to test the hypotheses that DOR is associated with SCA complications or hydroxyurea use.

This IRB-approved study occurred between 1 January 2018 and 31 March 2021. We included women with SCA, ages 19 to 30 years without polycystic ovarian syndrome who continued their routine care before the study visit. Informed consent was obtained, as per the Declaration of Helsinki. Ovarian reserve was measured on menstrual cycle days 3 to 5. To measure AMH, we used the Beckman Coulter Access 2 assay.[17] A reproductive endocrinologist (M.S.C.) quantified AFC by transvaginal or transabdominal ultrasound. We extracted data on disease severity and treatment adherence from the medical record. Subjects completed the Adult Sickle Cell Quality of Life Measurement (ASCQ-Me) Medical History Checklist and Pain Episodes Short Forms. We defined DOR using our clinical and published[7] standard as AMH $\leq$1.1 ng/mL $\pm$ FSH >10 to 40 IU.[16] Spearman's ρ test determined the correlation of AMH and AFC. We descriptively compared subject characteristics by age (19 to 25 vs 26 to 30 years) and DOR (yes/no) in the whole cohort and in the hydroxyurea-treated group. To determine associations with DOR, the Fisher exact and Mann-Whitney *U* tests were used for categorical and continuous variables, respectively. As this study is small, we compared DOR and hydroxyurea exposure in our cohort to published cohorts that included women <31 years with SCA.[7,9] We report the risk difference in DOR and numbers needed to harm (NNH) for subjects currently taking or not taking hydroxyurea and who ever or never took hydroxyurea. The statistical significance threshold was $P < .05$.

The cohort median age was 24 years (IQR 22, 28). Twenty-six subjects completed serologic measures, and 19 completed AFC measures before the COVID-19 pandemic shut down ultrasound visits. Two subjects had poor quality imaging. Among the 17 subjects with analyzable imaging, AFC was measured via transvaginal (n = 10) or transabdominal (n = 7) approach. Most subjects took hydroxyurea at some point (24/26). Current treatments were hydroxyurea (n = 15), chronic transfusions (n = 5), and supportive care (n = 6). Three subjects used hydroxyurea and chronic transfusions.

Descriptive comparisons are reported in Table 1. Expected age-associated decline in AMH occurred: AMH was higher among 19 to 25 than 26 to 30-year-olds (2.1ng/mL [IQR 1.7, 4.4]) vs 1.4 ng/mL [IQR 1.0, 2.0], $P = .03$). AMH correlated positively with AFC (Spearman's ρ 0.49, 95% CI: .40-.94, $P = .03$). Most subjects (21/26) did not have DOR. Subjects with and without DOR (n = 5 vs n = 21) had expected differences in AMH and FSH ($P < .01$), but not AFC ($P = .23$). There were no between-group differences in self-reported or abstracted disease complications (supplemental Table).

DOR was associated with hydroxyurea use: all subjects with DOR (n = 5) were taking hydroxyurea compared to 10 of 21 subjects without DOR who were taking hydroxyurea (5/5 vs 10/21, $P = .04$). Among subjects taking hydroxyurea (n = 15), DOR was associated with higher MCV (102 fl [IQR 100, 103] vs 92 fl [IQR 88, 99], $P = .03$), not absolute neutrophil count, hydroxyurea duration, hydroxyurea dose or disease complications (supplemental Figure). Table 2 compares DOR by hydroxyurea exposure in this Hopkins cohort and 2 previously published cohorts.[2,3] Only subjects "currently taking" or who "ever took" hydroxyurea had DOR. The NNH among those taking hydroxyurea was 3.0 (CI: 1.7, 10.6) in the Hopkins cohort and 4.1 (95% CI: 2.6, 10.4) in the Emory cohort.[9] Among those who ever took hydroxyurea, NNH was 4.8 (95% CI: 2.7, 21.8) in the Hopkins cohort and 1.9 (95% CI: 1.4, 3.0) in the Multicenter Study of Hydroxyurea.[7]

Table 1. Ovarian reserve in 26 young women considered by age, by presence or absence of DOR, and by presence or absence of DOR in the subgroup who reported taking hydroxyurea

	Cohort by age (n = 26)			Cohort by ovarian reserve (n = 26)			Subgroup taking hydroxyurea (n = 15)		
	19-25 y (n = 16)	26-30 y (n = 10)	*P* value	DOR (n = 5)	No DOR (n = 21)	*P* value	DOR (n = 5)	No DOR (n = 10)	*P* value
Median age (IQR), y	22.5 (21, 24)	28 (27, 29)	**<.01**	28 (27, 28)	24 (22, 26)	.12	28 (27, 28)	23 (21, 24)	.06
BMI, median (IQR)	25 (21, 24)	28 (27, 29)	.78	24 (21, 25)	25 (21, 26)	.63	24 (21, 25)	24 (21, 26)	.90
Hormonal contraception, n	6	3	.51	2	7	.58	2	3	.56
Disease complications									
ASCQ-Me medical history score	2 (0, 3)	2 (2, 4)	.5	2 (1, 3)	2 (1, 3)	.93	2 (1, 3)	2 (0, 3.5)	.68
ASCQ-Me pain frequency score	50 (44, 60)	54 (42, 56)	.75	44 (40, 44)	56 (48, 60)	.06	44 (40, 44)	52 (44, 55)	.18
Pain episodes in past 12 months	3 (2, 9)	7 (2, 8)	.88	5 (2, 7)	6 (2, 9)	.78	5 (2, 7)	6 (2, 9)	.63
Cerebrovascular disease, n	4	0	.12	0	4	.40	0	2	.43
Avascular necrosis, n	3	7	**.01**	3	7	.27	3	3	.28
Treatment history									
Current hydroxyurea, n	10	5	.41	5	10	**.04**	5	10	—
Ever hydroxyurea use, n	14	10	.36	5	19	.64	5	10	—
Current transfusions, n	5	3	.61	0	8	.12	0	3	.26
Supportive care, n	4	2	.58	0	6	.23	0	0	—
Hematologic characteristics									
Hemoglobin, g/dL	8.9 (8.2, 9.8)	9.3 (8.8, 9.9)	.57	8.9 (8.8, 10)	9 (8.3, 9.8)	.87	8.9 (8.8, 10)	8.5 (8.0, 8.9)	.30
Mean corpuscular volume, fL	89 (86, 98)	98 (89, 103)	.09	102 (100, 103)	89 (86, 97)	**.01**	102 (100, 103)	92 (88, 99)	**.03**
Absolute neutrophil count, K/μL	7.9 (4.3, 8.9)	5.1 (3.6, 8.2)	.25	3.7 (1.7, 8.2)	7.2 (4.6, 8.6)	.27	3.7 (1.7, 8.2)	7.6 (3.1, 9.2)	.33
Ferritin, ng/mL	466 (151, 1298)	602 (87, 1982)	1.00	259 (35, 398)	642 (205, 1982)	.11	259 (35, 398)	552 (232, 980)	.18

For the ASCQ-Me Medical History Short Form and Acute Pain Episodes Short Form lower score indicates better health. DOR is not associated with collected markers of disease severity. Median (IQR) is reported unless otherwise indicated. Bold values indicate statistical significance.

Table 1. (continued)

	Cohort by age (n = 26)			Cohort by ovarian reserve (n = 26)			Subgroup taking hydroxyurea (n = 15)		
	19-25 y (n = 16)	26-30 y (n = 10)	*P* value	DOR (n = 5)	No DOR (n = 21)	*P* value	DOR (n = 5)	No DOR (n = 10)	*P* value
Ovarian reserve measures									
Antimullerian hormone, ng/mL	2.1 (1.7, 4.4)	1.4 (1.0, 2.0)	**.03**	0.93 (0.9, 1.02)	2.02 (1.66, 3.58)	**<.01**	0.93 (0.9, 1.02)	2.54 (1.77, 3.58)	**<.01**
Antral follicle count, n	13 (8, 30)	9 (9, 12)	.46	7 (7, 7)	12 (9, 19)	.23	7 (7, 7)	13 (8, 24)	.28
Follicle stimulating hormone, IU	5.9 (4.5, 8.6)	10.1 (9.1, 11.3)	**<.01**	11.3 (10.1, 12)	6.8 (5.3, 9.2)	**<.01**	11.3 (10.1, 12)	5.7 (4.5, 7)	**<.01**
Estradiol, pg/mL	44 (32, 90)	41 (39, 53)	.83	32 (6, 53)	46 (33, 102)	.30	32 (6, 53)	46 (34, 95)	.22
Diminished ovarian reserve, n	1	4	.05	–	–	–	–	–	–

For the ASCQ-Me Medical History Short Form and Acute Pain Episodes Short Form lower score indicates better health. DOR is not associated with collected markers of disease severity. Median (IQR) is reported unless otherwise indicated. Bold values indicate statistical significance.

In this study of complete ovarian reserve measures in women with SCA, some young women had DOR, suggesting that counseling regarding fertility preservation is indicated for this population.[5] In subjects with DOR, median AFC was 7, a value associated with lower oocyte yield during oocyte harvest for preserving fertility or in vitro fertilization.[18] Addressing fertility before DOR onset will help optimize chances for future biological parenthood.

Here, DOR occurred in subjects currently taking hydroxyurea with evidence of treatment adherence by MCV, but not other treatment-related measures, as in previous studies.[7,9] However, a study of 50 older women with SCD (78% SCA, mean age 35.1 ± 5.9 years) included 8 hydroxyurea-treated subjects[6] with a mean AMH of 8.8 ± 8.3 pmol/L and although some subjects had reduced or negligible AMH, there was no association between hydroxyurea and AMH levels. These results are possibly confounded by the absence of an analysis adjusting for age and genotype. A larger study of well-phenotyped, age-, genotype- and treatment-stratified subjects is required for definitive conclusions about the effects of hydroxyurea on ovarian reserve and could address concerns about pre and postpubertal hydroxyurea initiation, reversibility, and even timing of fertility preservation interventions.

Even though we found no difference in disease complications by DOR status, the possibility that DOR, like hydroxyurea use, is a marker of SCA disease severity is not excluded. Even as data accrues to help refine the distinction between disease and treatment effect, the evidence presented here may inform practice.[19-21] For as evidence of hydroxyurea's benefits accumulates[22] and prescribing expands,[23,24] a growing number of adults with SCA will have had some hydroxyurea exposure. This study is useful for that population: among 102 young women with SCA, most (n = 84) had current or historic hydroxyurea exposure, and 32% of these subjects (n = 27/84) had DOR. Ideally, we would know whether optimized hydroxyurea use is causally associated with DOR or, since many hydroxyurea-exposed women did not have DOR, whether hydroxyurea use is only a proxy for SCA-associated risks for DOR. Absent definitive evidence, the shared decision-making process for hydroxyurea treatment provides a mechanism to address this uncertainty with patients and families.

This study's limitations include small size and that the relationship between DOR and pregnancy outcomes were not studied. Risks for DOR in young women with SCA and no hydroxyurea exposure could not be identified due to small numbers. Studies in compound heterozygous SCD with new SCA therapies and in prepubescent girls, along with those examining hydroxyurea's effects on fertility, oocyte quality, and pregnancy outcomes are also needed. Research teams from Europe, where fertility preservation is more accessible, may be poised to provide timely insights.[15,25]

This study describes a risk for DOR in some women with SCA. The presence of DOR is an accepted threshold for consideration of fertility preservation strategies.[11] This is a care standard for cancer patients,[10,26] but not for SCA. A proactive approach to caring for girls and women with SCA is to discuss fertility preservation. At present, inequitable access to fertility preservation limits fertility care.[12,25] This disparity leads to a treatment paradigm

Table 2. In 3 independent cohorts of young women with SCA, all subjects with DOR were exposed to hydroxyurea

	Currently taking hydroxyurea				"Ever took" hydroxyurea			
	Elchuri[18,*]		Hopkins[a]		Hopkins[b]		Multicenter Study of Hydroxyurea[5]	
Age range, years	10-21		19-30		19-30		20-30	
Median (IQR)	14.5 (2.5)†		24 (22, 28)		24 (22, 28)		29 (25, 29)	
	HU	**No HU**	**HU**	**No HU**	**Ever HU**	**No HU**	**Ever HU**	**No HU**
DOR	8	0‡	5	0‡	5	0‡	14	0‡
No DOR	25	14	10	11	19	2	13	2
Risk difference (95% CI)	0.24 (0.096, 0.39)		0.33 (0.095, 0.57)		0.21 (0.046, 0.37)		0.52 (0.33, 0.71)	
Number to harm (95% CI)	4.1 (2.6, 10.4)		3.0 (1.7, 10.6)		4.8 (2.7, 21.8)		1.9 (1.4, 3.0)	

Elchuri et al described DOR in adolescents with SCA taking hydroxyurea in their study.[8] Pecker et al described DOR in adult women with SCA in the Multicenter Study of Hydroxyurea.[7] The Multicenter Study of Hydroxyurea dataset precluded the possibility of determining whether hydroxyurea was being used at the time the samples used to measure AMH were procured, but data did identify whoever took hydroxyurea ("Ever took"). We compare subjects, dividing subjects by currently taking[a] or ever taking ("ever took") hydroxyurea[b]. No subjects without hydroxyurea exposure had DOR.

*Elchuri et al[18] measured AMH using Beckman-Coulter AMH Gen II ELISA and defined abnormally low AMH ("DOR") as <fifth percentile for age. Pecker et al[5] measured AMH using Esoterix (LabCorp) assay and defined DOR as AMH <1.1 ng/mL. In this study, we measured Beckman Coulter Access 2 assay and define DOR as AMH <1.1 ng/mL.

†Mean values with standard deviation are reported in this publication.

‡All subjects with DOR had hydroxyurea exposure. Conversely, there was no one without hydroxyurea exposure who had DOR.

that pits hydroxyurea, a transformative SCA treatment, against fertility, instead of coordinating treatment with fertility-preserving interventions.

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Authorship

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Footnotes

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