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Race-ethnic disparities in reproductive dysfunction in women with and without polycystic ovary syndrome

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ABSTRACT

Black and Hispanic women have disproportionately high rates of obesity and type 2 diabetes. However there is a lack of knowledge on race-ethnic differences in reproductive disorders such as polycystic ovary syndrome (PCOS). The objective of this study was to compare the prevalence of reproductive (irregular menses, oligomenorrhea, amenorrhea, infertility) and hyperandrogenic (HA) (hirsutism, acne) disorders in premenopausal women of diverse race-ethnicities with and without PCOS. Premenopausal women aged 18-50 years were identified in outpatient clinics in 2011 (n = 20,836) through retrospective chart review; 1,133 (5.4%) had PCOS. Race-ethnicity was self-reported and classified as: Black, Hispanic, White and Other (i.e. Asian/Pacific Islander, Native American/Alaskan and others). The diagnosis of reproductive and HA disorders was determined from the patient's chart. Statistical analyses for comparisons of groups included Chi^2 test, analysis of covariance (ANCOVA) and logistic regression (alpha = 0.05) (SAS v9.1). After adjusting for age and body mass index (BMI), overall, Black women had the highest burden of reproductive and HA disorders compared to other groups: irregular menses 8%, amenorrhea 5%, infertility 4%, hirsutism 2%, and acne 7% ($p < 0.05$, for all). Among women with PCOS, Black women consistently had the highest rates of reproductive and HA disorders including irregular menses (31%), amenorrhea (26%), infertility (19%), and hirsutism (17%) ($p < 0.05$, for all). Among women without PCOS, reproductive and HA disorders were low in all race-ethnicities (≤ 7%). Black women had the highest rates of irregular menses (7%) and acne (7%), while Other women had the highest rates of infertility (4%) ($p < 0.05$, for all). In conclusion, Black women with and without PCOS were diagnosed with more reproductive dysfunction than women of other race-ethnicities. Black women may be particularly susceptible to developing PCOS and may have more severe reproductive and HA phenotypes than women of other race-ethnicities.

KEYWORDS: polycystic ovary syndrome, reproductive dysfunction, race-ethnic disparities

INTRODUCTION

Health disparities represent a significant economic burden. Between 2003 and 2006, an estimated $1.24 trillion (in 2008 inflation-adjusted dollars) in medical care expenditures for African Americans, Asian Americans, and Hispanics were attributed to health inequalities [1]. Research suggests that people of minority race-ethnic backgrounds in the United States have less access to preventive care and as a result experience delays in diagnosis and more advanced disease at presentation [2] which may contribute to the added cost of care. Obesity and type 2 diabetes (T2D) are two examples of chronic diseases which disproportionately affect certain minority race-ethnic groups compared to Caucasians in the general population [2]. Addressing these disparities is a priority of the National Institutes of Health, which established the National Institute on

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Minority Health and Health Disparities (NIMHD) in 2010 [3], as well as a focus of The Endocrine Society which issued a scientific statement calling for more research exploring the underlying mechanisms contributing to race-ethnic disparities in endocrine disorders [2].

There is some evidence of race-ethnic differences in reproductive health [4]. Researchers have noted evidence of earlier puberty in Blacks, lower implantation and live birth rates with assisted reproductive technologies (ART) in Blacks compared with Caucasians, and differences in perimenopausal symptoms and timing of menopause in various racial-ethnic groups compared to Caucasians [3, 4]. Therefore, it would not be surprising if racial-ethnic differences extended to the reproductive endocrine disorder polycystic ovary syndrome (PCOS), a complex disease likely with both genetic and environmental factors influencing phenotypic expression [5, 6], that affects 5-10% of women [7-9]. For example, some race-ethnic groups may have higher rates of PCOS [10], with one study reporting the prevalence of PCOS in Black women at 8% compared to 5% in Caucasian women, although these were not statistically different [11]. In addition, Hispanic women living in Mexico have a PCOS prevalence of 6% [12], while Mexican American women living in the United States have almost double the risk with a population prevalence of 13% [13]. Although this could reflect differences in study design and methods, these differing prevalence estimates could also be attributed to variations in genetic susceptibility or environmental exposures for affected women. The few studies noting differences in the prevalence of PCOS by race-ethnicity (RE) and geographic location underscore the need for research into the underlying physiologic mechanisms which would allow for more targeted therapeutic strategies.

PCOS is traditionally characterized by biochemical or clinical manifestations (e.g. acne and hirsutism) of hyperandrogenism, ovulatory dysfunction, and the presence of polycystic ovaries [14, 15]. However, there is insufficient data evaluating whether race-ethnic background influences the clinical manifestations of PCOS [2]. Some reports suggest women of minority backgrounds have a more severe phenotype than Caucasians although the literature is mixed [16-19]. While these studies provide some insight into the possible race-ethnic differences in PCOS, they do not examine the role of race and ethnicity in more than two groups [16, 18] or have small sample sizes in the minority groups [17, 19]. Due to the paucity of information on race-ethnic differences in PCOS, with only a few studies evaluating disorders characteristic of PCOS in a control population [8, 20], there is a clear need for further research evaluating potential race-ethnic differences in PCOS phenotypes. The primary objective of this exploratory study was to compare the prevalence of reproductive disorders (irregular menses, oligomenorrhea, amenorrhea, infertility) and hyperandrogenic (HA) (hirsutism, acne) disorders in premenopausal women of diverse race-ethnicities, and furthermore, to compare the role of race-ethnicity in reproductive dysfunction in women with and without PCOS.

PATIENTS AND METHODS

Premenopausal women aged 18-50 years attending ambulatory clinics between January 1, 2011 and December 31, 2011 at Boston University Medical Center (BUMC) were identified (n = 20,836) through a retrospective chart review. BUMC is an urban medical center providing healthcare to an underserved population of diverse RE backgrounds, irrespective of medical insurance coverage. RE was self-reported and classified as Black, Hispanic, White, and Other. Women classified as Other (n = 3,326) included Asian/Pacific Islanders (n = 717), Native Americans (n = 49), women who self-reported as Other (n = 847), and women who declined or did not self-report a RE (n = 713). PCOS cases (n = 1,133) were identified by chart review in our institution's electronic medical record (EMR). PCOS status was determined by physician diagnosis of PCOS as detailed in the patient's chart. This study protocol was approved by the BUMC Institutional Review Board.

Reproductive and HA disorders were determined by reviewing the medical records of the patients. BUMC's EMR lists diagnoses in the medical record with their ICD9 code. The reproductive and HA disorders were irregular menses (ICD9 626.4), oligomenorrhea (ICD9 626.1), amenorrhea (ICD9 626.0), infertility (ICD9 628), hirsutism (ICD9 704.1), and acne (ICD9 706.0-706.1). The rates of reproductive and HA disorders were compared

across race-ethnic groups of premenopausal women. Comparisons across groups were done using Chi-square test for categorical variables and independent t-tests or analysis of variance (ANOVA) for continuous variables with additional post hoc testing between pairs of groups with independent t-tests (Bonferroni/DUNN method) for statistically significant findings. ANCOVA and logistic regression were used to control for potential confounding by age and BMI. Analyses adjusting for BMI were limited to the 89% of women that had a recorded BMI in their chart.

The effect of PCOS status on risk of reproductive dysfunction was analyzed with contingency tables and logistic regression allowing adjustment for age and BMI. Potential interaction between RE and PCOS status in relation to reproductive and HA disorders was investigated using logistic regression models. Given the positive interaction between RE and PCOS status, analyses of the association of RE and reproductive and HA outcomes were stratified by PCOS status. Analyses were completed using SAS v 9.1 (SAS Institute Inc., Cary, NC). Alpha was set at 0.05 for the purpose of determining statistical significance.

RESULTS

Premenopausal women seen in BUMC ambulatory clinics in 2011 had a mean age of 33 ± 9 years with a mean BMI of 30 ± 8 kg/m^2 (Table 1). Age and BMI varied by RE, with Black and Hispanic women having the highest BMI (31 ± 8 kg/m^2). Black women had the highest systolic (120 ± 14 mmHg) and diastolic (76 ± 9 mmHg) blood pressure, even after adjusting for age and BMI (Table 1).

The prevalence of reproductive and HA disorders varied by RE (Table 2). Overall, Black women had the most irregular menses (8%), amenorrhea (5%),

Table 1. Characteristics of women seen in the ambulatory clinics (n = 20,836) at BUMC by race-ethnicity; unadjusted data is presented as mean ± SD or n (%). Adjusted data is presented as adjusted mean ± adjusted SD.

	Pre-menopausal women n = 20,836	B n = 8,791	H n = 3,728	W n = 4,991	O n = 3,326	p-value
Age (years)[a]	33 ± 9	33 ± 9	33 ± 9	33 ± 9	34 ± 9	< 0.0001
BMI (kg/m^2)[a,b]	30 ± 8	31 ± 8	31 ± 8	28 ± 8	28 ± 8	< 0.0001
SBP (mmHg)[a,b]	119 ± 15	120 ± 14	117 ± 14	119 ± 14	117 ± 14	< 0.0001
DBP (mmHg)[a,b]	76 ± 10	76 ± 9	75 ± 9	76 ± 9	75 ± 9	< 0.0001
PCOS	1133 (5%)	383 (4%)	182 (5%)	315 (6%)	253 (8%)	< 0.0001
Education[b]						
< High School (HS)	5790 (31%)	2912 (36%)	1400 (43%)	674 (15%)	804 (31%)	< 0.0001
HS or GED	8624 (47%)	4033 (49%)	1398 (43%)	2085 (47%)	1108 (43%)	
College	4065 (22%)	1255 (15%)	481 (15%)	1654 (37%)	675 (26%)	
Insurance[b]						
Private	7184 (39%)	2332 (29%)	701 (23%)	2818 (60%)	1333 (47%)	< 0.0001
Government	9249 (50%)	4619 (58%)	1852 (60%)	1737 (37%)	1041 (37%)	
None	2187 (12%)	1022 (13%)	526 (17%)	171 (4%)	468 (16%)	

[a]Given the 1 year age difference between groups, mean levels of other characteristics by RE group were adjusted for age. SBP and DBP by RE were additionally adjusted for BMI. [b]Data on BMI was available for 90% of Black women, 83% Hispanics, 84% Whites and 84% Other women. Systolic blood pressure was available for 95% of Black women, 89% Hispanics, 93% white women and 91% Other women. Diastolic blood pressure was available for 95% of Black women, 89% Hispanics, 92% White women and 91% of Other women. Education information was available for 93% of Black women, 88% of Hispanics, 88% of White women and 78% of Other women. Insurance information was available for 91% of Black women, 83% of Hispanics, 95% of White women and 85% of Other women. B = Black women, W = White women, H = Hispanic women, O = Other women and GED = General Educational Development; GED is a high school equivalency certificate.

infertility (4%), hirsutism (2%), and acne (7%). Other women had the second highest burden of reproductive disorders: irregular menses (7%), oligomenorrhea (2%), amenorrhea (5%), infertility (4%), hirsutism (2%), and acne (6%). Logistic regression models were used to examine the risk of reproductive and HA disorders by RE adjusted for age and BMI which did not change the results (Wald Chi^2 statistic in Table 2). Post hoc analysis of differences between RE groups showed that Black women had greater risk for most reproductive and HA disorders than White women while Other women only had a higher risk of infertility compared to White women (Table 2).

PCOS status

Women with PCOS were on average 2 years younger than women without PCOS (31 ± 7 vs. 33 ± 9 years, $p < 0.0001$; Table 3) and were more likely to be college educated (27% vs. 22%, $p < 0.0001$; data not shown) compared to women without PCOS. The age adjusted mean BMI was higher in women with PCOS (35 ± 8 vs. 30 ± 8 kg/m^2, $p < 0.0001$). Age and BMI adjusted systolic blood pressure (SBP) was not significantly different between groups (119 ± 14 vs. 119 ± 14 mmHg, $p = 0.5$) although age and BMI adjusted diastolic blood pressure (DBP) was higher in women with PCOS (77 ± 9 vs. 76 ± 9 mmHg, $p = 0.005$) (Table 3). As expected, women with PCOS had higher rates of all reproductive and HA disorders compared to women without PCOS ($p < 0.0001$ for all). Odds ratios (OR) adjusted for age and BMI showed women with PCOS had increased risk of irregular menses [OR 5.8, 95% confidence interval (CI): 4.7-7.1], oligomenorrhea (OR 11.9, 95% CI: 8.6-16.7), amenorrhea (OR 8.1, 95% CI: 6.5-10.2), and infertility (OR 8.4, 95% CI: 6.4-11.0). Women with PCOS also had higher rates of HA disorders including hirsutism (OR 15.4, 95% CI: 11.5-20.6) and acne (OR 2.6, 95% CI: 2.0-3.4) compared to women without PCOS (Table 3).

PCOS status and race-ethnicity

In women with PCOS, age ($p = 0.1$) and BMI ($p = 0.2$) were similar across race-ethnic groups; therefore data were not adjusted for these characteristics (Table 4). Among women with PCOS, Black and Hispanic women had a lower educational level compared to the other groups: 79% of Black women, 77% of Hispanic women, 66% of White women, and 67% of Other women had a high school degree or less ($p < 0.0001$; data not shown). Among women without PCOS, women

Table 2. Reproductive and hyperandrogenic conditions by RE in women at BUMC (n = 20,836); data presented as n (%).

	B n = 8,791	H n = 3,728	W n = 4,991	O n = 3,326	Chi^2 p-value	Wald Chi^2 p-value[a]	OR[a] (95% CI) B vs. W	OR[a] (95% CI) H vs. W	OR[a] (95% CI) O vs. W
Irregular menses	678 (8%)	232 (6%)	297 (6%)	228 (7%)	0.0003	0.01	1.3 (1.1-1.5)	1.1 (0.9-1.3)	1.2 (1.0-1.5)
Oligomenorrhea	127 (1%)	40 (1%)	55 (1%)	54 (2%)	0.07	0.3	1.0 (0.7-1.5)	0.8 (0.5-1.2)	1.3 (0.8-2.0)
Amenorrhea	450 (5%)	133 (4%)	214 (4%)	160 (5%)	0.001	0.0005	1.2 (1.0-1.5)	0.8 (0.6-1.0)	1.2 (1.0-1.5)
Infertility	342 (4%)	93 (2%)	97 (2%)	145 (4%)	< 0.0001	< 0.0001	2.1 (1.6-2.7)	1.1 (0.8-1.6)	2.2 (1.7-3.0)
Hirsutism	164 (2%)	46 (1%)	67 (1%)	53 (2%)	0.03	0.04	1.4 (1.0-2.0)	0.9 (0.6-1.4)	1.4 (0.9-2.2)
Acne	635 (7%)	147 (4%)	271 (5%)	191 (6%)	< 0.0001	< 0.0001	1.5 (1.3-1.8)	0.9 (0.7-1.1)	1.2 (1.0-1.4)

[a]Logistic Regression Wald Chi^2 statistic and Odds ratios (ORs) are adjusted for age and BMI. B = Black women, W = White women, H = Hispanic women, O = Other women.

Table 3. Characteristics of women seen in the ambulatory clinics (n = 20,836) at BUMC by PCOS status; differences in rates of reproductive dysfunction with the odds of having reproductive disorders in women with PCOS compared to women without PCOS is presented (Panel 2)[a].

Characteristics by PCOS status					
	n = 20,836	**PCOS n = 1,133**	**Non-PCOS n = 19,703**	**p-value**	
Age (years)[b]	33 ± 9	31 ± 7	33 ± 9	< 0.0001	-
BMI (kg/m^2)[b,c]	30 ± 8	35 ± 8	30 ± 8	< 0.0001[a]	-
SBP (mmHg)[b,c]	119 ± 15	119 ± 14	119 ± 14	0.5[a]	-
DBP (mmHg)[b,c]	76 ± 10	77 ± 9	76 ± 9	0.005[a]	-
Reproductive dysfunction by PCOS status					
	n = 20,836	**PCOS n = 1,133**	**Non-PCOS n = 19,703**	**Chi^2 p-value**	**OR (95% CI)**[d]
Irregular menses	1435 (7%)	230 (20%)	1205 (6%)	< 0.0001	5.8 (4.7-7.1)
Oligomenorrhea	276 (1%)	103 (9%)	173 (1%)	< 0.0001	11.9 (8.6-16.7)
Amenorrhea	957 (5%)	211 (19%)	746 (4%)	< 0.0001	8.1 (6.5-10.2)
Infertility	677 (3%)	156 (14%)	521 (3%)	< 0.0001	8.4 (6.4-11.0)
Hirsutism	330 (2%)	137 (12%)	193 (1%)	< 0.0001	15.4 (11.5-20.6)
Acne	1244 (6%)	122 (11%)	1122 (6%)	< 0.0001	2.6 (2.0-3.4)

[a]Unadjusted data is presented as mean ± SD or n (%). Adjusted data is presented as adjusted mean ± adjusted SD. [b]Given the 2 year difference in age between groups, mean levels of other characteristics by PCOS status were adjusted for age. SBP and DBP by PCOS status were additionally adjusted for BMI. [c]Data on BMI was available in 45% of women with PCOS and 89% of women without PCOS. [d]Odds ratios are adjusted for age and BMI.

in the Other group were slightly older (34 ± 9 years), and Black (31 ± 8 kg/m^2) and Hispanic (31 ± 8 kg/m^2) women had higher mean BMI compared to the other groups (Table 4, p < 0.0001). Similar to women with PCOS, a higher percentage of Black and Hispanic women without PCOS had a high school degree or less compared to the other two groups (Black: 85%, Hispanic: 86%, White: 62% and Other: 74%, p < 0.0001; data not shown). Age adjusted mean BMI, SBP and DBP were similar to unadjusted levels. Black women had the highest SBP (120 ± 14 mmHg, p < 0.0001), and Black and White women had higher DBP (76 ± 9 mmHg, p < 0.0001) (Table 4).

PCOS status varied by RE with Other women having the highest rates of PCOS (8%), followed by White women (6%) and Black women (5%) (Table 1, p < 0.0001). Since reproductive and HA disorders varied by RE as well as PCOS status, a potential interaction between PCOS status and RE was analyzed by adding an interaction term to the multiple logistic regression models. There was a significant interaction between RE and PCOS status for irregular menses (p < 0.0001) and amenorrhea (p = 0.04) but not for all reproductive and HA disorders. We therefore stratified the analyses by PCOS status to examine the role of RE and reproductive dysfunction in women with and without PCOS.

The prevalence of reproductive and HA disorders varied by RE in women with and without PCOS. Black women with PCOS consistently had the highest rates of reproductive and HA disorders: irregular menses 31%, amenorrhea 26%, infertility 19% and hirsutism 17% (p < 0.05 for all). Black women with PCOS also had the highest rates of oligomenorrhea (12%, p = 0.05) and acne (13%, p = 0.08), but differences across REs only trended toward significance. When comparing the odds of having reproductive and HA disorders across RE, Black women consistently had increased odds of having reproductive and HA disorders compared to White women except for acne (OR 1.2, 95% CI: 0.8-1.9). In contrast, Hispanic and Other women

Table 4. Characteristics of women seen in the ambulatory clinics (n = 20,836) at BUMC by race and PCOS status; unadjusted data is presented as mean ± SD. Adjusted data is presented as adjusted mean ± adjusted SD.

	PCOS (n = 1,133)					Non-PCOS (n = 19,703)					
	B n = 383	**H n = 182**	**W n = 315**	**O n = 253**	**p-value**	**B n = 8,408**	**H n = 3,546**	**W n = 4,676**	**O n = 3,073**	**p-value**	**Adj p-value[a]**
Age (years)[a]	31 ± 7	32 ± 7	32 ± 7	31 ± 7	0.1	33 ± 9	33 ± 9	33 ± 9	34 ± 9	< 0.0001	-
BMI (kg/m^2)[b]	36 ± 10	35 ± 9	34 ± 9	34 ± 10	0.2	31 ± 8	31 ± 8	28 ± 8	28 ± 7	< 0.0001	-
Age Adj BMI[a]	-	-	-	-	-	31 ± 8	31 ± 8	28 ± 8	28 ± 8	-	< 0.0001
SBP (mmHg)	122 ± 16	118 ± 12	121 ±14	120 ± 16	0.1	120 ± 16	118 ± 14	118 ± 14	116 ± 15	< 0.0001	-
Age/BMI Adj SBP[a]	-	-	-	-	-	120 ± 14	117 ± 14	119 ± 14	117 ± 14	-	< 0.0001
DBP (mmHg)	79 ± 12	77 ± 8	77 ± 9	77 ± 9	0.5	77 ± 10	75 ± 9	75 ± 9	74 ± 9	< 0.0001	-
Age/BMI Adj DBP[a]	-	-	-	-	-	76 ± 9	75 ± 9	76 ± 9	75 ± 9	-	< 0.0001

[a]Given the 2 year difference in age, characteristics adjusted for age. SBP and DBP were additionally adjusted for BMI. [b]Data on BMI was available for 55% of Black women, 42% of Hispanic women, 41% of white women and 36% of Other women with PCOS. In women without PCOS, BMI data was available for 94% of Black women, 85% of Hispanic women and 87% of white and Other women. B = Black women, W = White women, H = Hispanic women, O = Other women Adj = adjusted.

had similar risk for reproductive and HA disorders as White women (Table 5).

Overall, women without PCOS had low rates of reproductive and HA disorders (≤ 7%). Similar to Black women with PCOS, Black women without PCOS had the highest rates of irregular menses (7%, p = 0.02), hirsutism (1.2%, p = 0.03), and acne (7%, p < 0.0001). Hispanic women had slightly lower rates of amenorrhea compared to the other three groups (3% vs. 4%, p = 0.0003). Other women had the highest rate of infertility (4%, p < 0.0001). After adjusting for age and BMI, Black (OR 2.1, 95% CI: 1.6-2.8) and Hispanic women (OR 2.4, 95% CI: 1.7-3.3), without PCOS had higher risk of infertility compared to Caucasians, while Black women had an increased risk of acne (OR 1.5, 95% CI: 1.3-1.8), compared to Caucasians (Table 6).

DISCUSSION

The prevalence of reproductive dysfunction varied by RE in premenopausal women overall, with Black women having the most reproductive dysfunction at our urban medical center. As expected, PCOS status was associated with greater risk of all reproductive and HA disorders even after adjustment for age and BMI. Black women with PCOS had the highest rates of reproductive and HA disorders. Although women without PCOS had relatively low rates of reproductive dysfunction overall (< 10%), Black women still had the greatest burden of reproductive and HA disorders.

Potential reasons for RE disparities in chronic diseases such as PCOS include genetic variation [21], epigenetic differences [3], environmental influences, socioeconomic status, differences in individual risk behaviors, inadequate access to health care, and cultural issues such as discrimination [2]. Health disparities may have economic implications [1, 22] and affect the quality of life and health of women with PCOS across the lifespan [4]. Further research with well-designed studies including in-depth phenotyping of women with PCOS from varied race-ethnic backgrounds is needed to determine the extent of and consequences of RE disparities in women with PCOS given the associated

Table 5. Reproductive and hyperandrogenic conditions in women with PCOS (n = 1133) at BUMC; data presented as n (%).

	B n = 383	H n = 182	W n = 315	O n = 253	Chi^2 p-value	OR (95% CI) B vs W	OR (95% CI) H vs W	OR (95% CI) O vs W
Irregular menses	118 (31%)	33 (18%)	42 (13%)	37 (15%)	< 0.0001	2.9 (2.0-4.3)	1.4 (0.9-2.4)	1.1 (0.7-1.8)
Oligomenorrhea	46 (12%)	15 (8%)	19 (6%)	23 (9%)	0.05	2.1 (1.2-3.7)	1.4 (0.7-2.8)	1.6 (0.8-2.9)
Amenorrhea	100 (26%)	37 (20%)	49 (16%)	25 (10%)	< 0.0001	1.9 (1.3-2.8)	1.4 (0.9-2.2)	0.6 (0.4-1.0)
Infertility	74 (19%)	29 (16%)	23 (7%)	30 (12%)	< 0.0001	3.0 (1.9-5.0)	2.4 (1.3-4.3)	1.7 (1.0-3.0)
Hirsutism	64 (17%)	18 (10%)	34 (11%)	21 (8%)	0.006	1.7 (1.1-2.6)	0.9 (0.5-1.7)	0.7 (0.4-1.3)
Acne	51 (13%)	12 (7%)	36 (11%)	23 (9%)	0.08	1.2 (0.8-1.9)	0.5 (0.3-1.1)	0.8 (0.4-1.3)

B = Black women, W = White women, H = Hispanic women, O = Other women, OR = odds ratio.

Table 6. Reproductive and hyperandrogenic conditions in women without PCOS (n = 19,703) at BUMC; data presented as n (%).

	B n = 8,408	H n = 3,546	W n = 4,676	O n = 3,073	Chi^2 p-value	OR[a] (95% CI) B vs W	OR[a] (95% CI) H vs W	OR[a] (95% CI) O vs W
Irregular menses	560 (7%)	199 (6%)	255 (5%)	191 (6%)	0.02	1.2 (1.0-1.4)	1.1 (0.9-1.3)	1.2 (1.0-1.4)
Oligomenorrhea	81 (1%)	25 (1%)	36 (1%)	31 (1%)	0.4	1.1 (0.7-1.7)	0.9 (0.5-1.5)	1.2 (0.7-2.1)
Amenorrhea	350 (4%)	96 (3%)	165 (4%)	135 (4%)	0.0003	1.2 (1.0-1.5)	0.8 (0.6-1.0)	1.3 (1.0-1.6)
Infertility	268 (3%)	64 (2%)	74 (2%)	115 (4%)	< 0.0001	2.1 (1.6-2.8)	1.1 (0.8-1.6)	2.4 (1.7-3.3)
Hirsutism[b]	100 (1.2%)	28 (0.8%)	33 (1.0%)	32 (0.7%)	0.03	1.5 (1.0-2.3)	1.1 (0.6-1.8)	1.6 (1.0-2.7)
Acne	584 (7%)	135 (4%)	235 (5%)	168 (5%)	< 0.0001	1.5 (1.3-1.8)	0.9 (0.7-1.1)	1.2 (1.0-1.5)

[a]Odds ratios control for age and BMI. [b]Percent values were expanded to the tenth decimal position for non-PCOS women for clarity, given that there was a statistically significant finding at very low percent levels in some groups for Hirsutism. B = Black women, W = White women, H = Hispanic women, O = Other women, OR = odds ratio.

negative impact on quality of life and psychological, reproductive, metabolic and cardiovascular health [14, 23].

The prevalence of hirsutism is estimated to be 5-15% in the general population [14] with rates as high as 70-75% in women with PCOS [23, 24]. Although some studies suggest no RE differences in the prevalence of hirsutism [25, 26], we found RE differences in hirsutism in this cohort with Black women having higher rates of hirsutism compared to the other racial-ethnic groups in women both with (17% vs. 8-11%, p = 0.006) and without (1.2% vs.

0.7-1.0%, $p < 0.0001$) PCOS (Table 4). The finding of RE differences in hirsutism is consistent with known RE differences in biology and is reflective of current expert opinion. Chinese women have lower rates of hirsutism compared to Caucasians due to lower 5-α reductase activity, the enzyme that converts testosterone to the more potent androgen dihydrotestosterone, in the skin at the hair follicle [27]. Furthermore, the Androgen-Excess Society has acknowledged that there are racial-ethnic differences in terminal hair growth and recommends using population-specific modified Ferriman-Gallwey (mFG) hirsutism score cutoffs. The lowest thresholds are for Chinese women and the highest thresholds are for Middle Eastern, Mediterranean, and Mexican women [28].

Using RE-specific mFG cutoffs for hirsutism, researchers found that Chinese women with PCOS present more frequently with hirsutism compared to Caucasians [18]. Other research suggests Middle East women with PCOS are more hirsute compared to Caucasians [16] and Hispanics have a tendency toward a significantly higher mFG hirsutism score compared to non-Hispanics ($p = 0.06$) [17]. Interestingly, Icelandic Caucasian women with PCOS had a lower FG hirsutism score (7.1 vs. 15.4, $p < 0.0001$) and a lower percentage of hirsutism (48% vs. 74%, $p < 0.0001$) compared to Caucasians from Boston, suggesting place of residence, genetics and other factors may play a role in the phenotypic expression of hirsutism [19]; however, this study reported no RE differences in hirsutism overall among Caucasians (n = 172), Blacks (n = 44), Hispanics (n = 25), and Asians (n = 21) [19]. Our study, which found Black women with PCOS had the highest rates of hirsutism compared to other groups, may have greater statistical power given the higher number of women across the four RE groups studied. Our findings support a need to consider RE when evaluating hirsutism [28], the most widely used clinical criterion for hyperandrogenism [11].

Acne, a less reliable marker of hyperandrogenism, has an estimated prevalence of 12% in the general population [29] and 14-25% in women with PCOS [14]. Reports of RE differences in acne are inconsistent. One study reported significantly higher rates of acne in Southeast Asians (n = 47) compared to Caucasians (n = 40) [30], while another found no significant difference between Asians (n = 28) and Caucasians (n = 121) [31]. The discrepant reports may reflect environmental factors since Caucasian women with PCOS living in Boston have a significantly higher rate of acne compared to Icelandic Caucasians (85% vs. 62%, $p < 0.0001$) [19] or they could be due to the small sample size in these studies. At BUMC, Black women with (13% vs. 7-11%, $p = 0.08$) and without PCOS (7% vs. 4-5%, $p < 0.0001$) had higher rates of acne compared to women in other RE groups.

There is evidence of RE differences in reproductive health, beginning as early as puberty. Black girls enter puberty earlier than Caucasian girls and Black women report greater perimenopausal symptoms and enter menopause earlier than Caucasian women [4]. Although there are some reports that there are RE differences in PCOS prevalence, there are surprisingly very few studies of RE differences in reproductive function in women with PCOS given that PCOS is the most common cause of ovulatory dysfunction [14] and 75-85% of women with PCOS have menstrual dysfunction [24]. One study reported that Asian women with PCOS had higher rates of oligomenorrhea compared to Caucasian women [31], while another study found Chinese women presented with amenorrhea more often than Dutch Women [18]. In one of the few studies to examine the role of RE in multiple groups of women with PCOS, researchers found that Caucasian women, who comprised 70% of the population, had higher rates of ovulatory dysfunction compared to African Americans, Asians, and American Indian/Alaskan Native women (84% vs. 60-76%, $p < 0.001$) [17]. In our study, Black women with PCOS had higher rates of irregular menses and amenorrhea compared to the other three groups, while Black women without PCOS had higher rates of irregular menses, oligomenorrhea, and amenorrhea compared to the other three groups. Our data suggest RE differences in menstrual function exist and strongly support the need for research to elucidate the underlying mechanisms which may define therapeutic targets to reduce disparities in reproductive health.

RE disparities related to infertility treatment have been reported [32, 33]. Black women received treatment for infertility later than Caucasian women, even in a state with mandated coverage for infertility treatment [32]. Once undergoing assisted reproductive

technology with fresh embryos, Black women experienced fewer live births compared to white women, though there was no significant difference in cycles using cryopreserved embryos [33]. These RE disparities in infertility most likely carry over into the PCOS population where approximately 50% of women with PCOS have primary infertility and 25% have secondary infertility [14]. In fact, our study found Black women with and without PCOS had some of the highest rates of infertility, higher than Caucasian women.

This study has several strengths. Notably, our research study builds on previous literature by providing an evaluation of RE differences in reproductive and HA conditions across four racial-ethnic groups both with and without PCOS. Furthermore, the effect of inadequate access to healthcare due to lack of insurance is mitigated in our clinic population by near-universal health insurance coverage in Massachusetts [2]. Finally, we relied on clinician diagnoses as opposed to self-reported data. However, this study has several limitations. We were unable to report data for some RE subgroups such as Asian, Middle Eastern, Native American or Alaskan subgroups due to very small numbers of women in these groups. In addition, there was the potential for misclassification of clinical disorders if the diagnoses were not consistently added to the problem list in our electronic medical record. For instance, we may have missed PCOS cases if the condition was not coded by the clinician. Furthermore, we were unable to confirm what criteria the clinician used to make the diagnosis of PCOS. However, the 5.4% prevalence of PCOS in our clinic population is in the estimated range of true population prevalence between 5 and 10% [7-9]. We also could not evaluate if the degree of androgen elevation influenced differences in reproductive and HA conditions because < 10% of women had hormone data available. Nonetheless, this study provides important evidence of RE disparities in reproductive dysfunction with Black women presenting with higher rates of reproductive and HA disorders compared to other RE groups in women both with and without PCOS. Our findings underscore a need for more multi-level research investigating the underlying mechanisms contributing to these RE differences in reproductive health in women with and without PCOS.

CONCLUSION

Clinicians should be aware of race-ethnic disparities in reproductive and HA disorders in women, particularly women with PCOS. Overall, Black women with and without PCOS had more reproductive dysfunction than women from other race-ethnic groups. Black women may be particularly susceptible to developing PCOS. This exploratory analysis from a diverse, urban clinic population provides insight into potential RE differences in reproductive and HA conditions associated with PCOS and underscores the need for further research with well-designed studies including in-depth phenotyping of women with PCOS from varied race-ethnic backgrounds.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

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