Edward E. Wallach, M.D.
Associate Editor

Racial and ethnic differences in reproductive potential across the life cycle

Samantha F. Butts, M.D., MSCE.[a] *and David B. Seifer, M.D.*[b,c]

[a]Division of Infertility and Reproductive Endocrinology, University of Pennsylvania Medical School, Philadelphia, Pennsylvania; [b]Genesis Fertility and Reproductive Medicine, Maimonides Medical Center, Brooklyn, New York; [c]Obstetrics, Gynecology and Reproductive Sciences, Mt. Sinai School of Medicine, New York, New York

Objective: To review variations in specific reproductive health outcomes by race and ethnicity. A growing number of reports have explored potential gaps in the quality of reproductive health and healthcare across racial and ethnic groups. Diverse results from numerous investigations have made it challenging for practitioners to confirm the significance of these disparities.

Method(s): Three specific areas of the reproductive life cycle were examined: pubertal onset, outcomes from treatment with assisted reproductive technologies (ART), and the menopausal transition. These areas were selected as they encompass a continuum of events across the reproductive life span of women. Outcomes were compared in black, white, Asian, and Hispanic women. Medline searches querying on keywords puberty, IVF, ART, menopause, menopausal symptoms, racial disparity, race, Asian, Japanese, Chinese, African American, black, Hispanic, and Latino were performed to isolate relevant publications for review.

Result(s): Differences across race and ethnicity were noted in each clinical endpoint. The most notable findings included earlier puberty in blacks and Hispanics compared with whites, significantly lower live birth rates after ART in all racial and ethnic groups compared with whites, and differences in perimenopausal symptomatology and possibly timing in various racial/ethnic groups compared with whites. Additional research is needed to completely unravel the full significance and basic underpinnings of these disparities. Some of the limitations of the current state of the literature in drawing conclusions about the independent effect of race/ethnicity on reproductive disparities include small samples sizes in some studies, inconsistencies in the characterization of racial/ethnic groups, and incomplete control of potential confounding.

Conclusion(s): Race and ethnicity appear to be important correlates of outcomes from the initiation of reproduction functioning through to its conclusion. The ultimate goal of identifying racial disparities in reproduction is to isolate the basic determinants of disparities and formulate strategies to improve outcomes for women at risk. The differences demonstrated in this review of the literature could represent environmental, sociocultural, and/or genetic correlates of race that influence these important milestones. (Fertil Steril® 2010;93:681–90. ©2010 by American Society for Reproductive Medicine.)

Key Words: Health disparities, race, racial disparities, reproductive aging, menopause, puberty, ART outcomes, black women, Asian women, Hispanic women

Differences in multiple health indicators have been shown to vary by race and ethnicity. Diabetes mellitus, coronary artery disease and perinatal mortality, for instance, disproportionately impact certain ethnic and racial groups compared to white individuals (1–6). These differences have been deemed health disparities precisely because they represent gaps in the quality of health and healthcare across racial and ethnic groups. Health disparities research has shed light on some of the underpinnings of these differences, and in so doing, has aimed to reduce morbidity in individuals at risk.

Despite the apparent significance of describing health disparities, this area of research has been fraught with challenges. Some critics describe difficulties in accurately categorizing individuals into discrete racial categories (5–8). Appropriate racial and ethnic classification is critical to study validity, especially when race is used as a surrogate for genetic correlates of disease. It has been argued that racial admixture has increased markedly over time, making attempts at strict racial categorization increasingly confusing and potentially outdated. Finally, there is a concern that identifying health disparities could reinforce deleterious stereotypes about groups and further marginalize the very individuals suffering from the disparities (7, 8).

Received October 27, 2009; accepted October 27, 2009; published online November 25, 2009.
S.F.B. has nothing to disclose. D.B.S. receives royalties related to the use of Mullerian inhibiting substance/Anti-mullerian hormone for predicting ovarian response in women with infertility.
Reprint requests: Samantha Butts, M.D., MSCE, 3701 Market Street, Suite 800, Philadelphia, PA 19104 (FAX: 215-349-5512; E-mail: sbutts@obgyn.upenn.edu).

Differences in reproductive outcomes across racial and ethnic groups have been described in a growing number of reports. Differences have been demonstrated in pubertal timing, in outcomes after treatment with assisted reproductive technologies (ARTs), and in reproductive aging. In this review, we aim to present and critically appraise the existing data in several areas where differences in reproductive outcomes between racial and ethnic groups have been described. Although the volume of data comparing reproductive outcomes between blacks and whites is greatest, we will describe outcomes in four major racial/ethnic groups: whites, blacks, Asians, and Hispanics. In the reports reviewed, the white racial category is used as a reference against which other categories are compared. In this analysis, we examined disparities in reproductive health indicators in women across the life span.

PUBERTY

From the beginning of female reproductive development, differences in functioning can be found by race and ethnicity. Data from large cross-sectional studies have demonstrated that, on average, black girls initiate puberty 1 year earlier than white girls (9–14). One of these investigations, a cross-sectional study of over 17,000 children (10% of the sample was black, 90% white) conducted by the American Academy of Pediatrics showed that all pubertal milestones were achieved earlier in black children compared with whites, controlling for height and weight (10). The average age of thelarche in blacks was 8.87 years compared with 9.96 years in whites ($P<.001$) and menarche occurred at a mean age 12.16 years in black children compared with 12.88 years in white children (10). Similar differences in attainment of pubertal milestones between black and white children were found in data from the third National Health and Nutrition Examination Survey (NHANES). This report also described developmental outcomes in Mexican–American children and concluded that, in general, black children initiate puberty earliest (mean age of pubarche 9.5 years; mean age of adrenarche 9.5 years; mean age of menarche 12.2 years), followed by Mexican–American children (mean age of pubarche 9.8 years; mean age of adrenarche 10.3 years; mean age of menarche 12.2 years) and then white children (mean age of pubarche 10.3 years; mean age of adrenarche 10.5 years; mean age of menarche 12.7 years) (9). In the NHANES report, the association between race/ethnicity and initiation of puberty was significant after adjusting for age, current body mass index (BMI), and socioeconomic status; controlling for BMI, however, attenuated the significant relationship between race/ethnicity and age of menarche (9).

Data concerning pubertal timing in Asian children compared with other races is limited and conflicting. In one report, a multiethnic cohort of 1,378 girls in California ages 8 to 13, Asian/Pacific Island children initiated menarche significantly earlier than white children after controlling for age, height, and BMI (15). The median age of menarche in Asian/Pacific Island children was 12.2 years compared with 12.8 years in whites. Conversely, other reports examining pubertal milestones have demonstrated that Asian children mature less rapidly than whites and Hispanics (16, 17).

The underlying reason for discrepant timing in puberty across racial/ethnic strata is not fully understood, but several theories have been proposed. The age of menarche for all children in the United States gradually declined over 20th century, a fact primarily attributed to improved nutrition and increasing trends in childhood weight (18). A prevailing theory suggests that a critical threshold of body weight and total fat mass must be achieved to initiate menarche (19, 20). A consistent but refined version of this theory is that the amount of gynecoid fat mass is associated the onset of menarche (21).

Differences in body habitus between racial/ethnic groups have been demonstrated in adults (22) and in adolescents (15, 23), and could mediate distinct patterns of pubertal timing.

An important controversy in this area surrounds the question of timing: do differences in fat mass mediate the onset of puberty or do pubertal changes drive disparate fat patterns across race and ethnicity? Part of the challenge in answering this question has to do with the abundance of cross-sectional data describing relationships between body habitus and pubertal milestones. One such report from a cross-section of children surveyed in NHANES III demonstrated a significant association between menarche and gluteofemoral fat mass (but did not specifically report on race/ethnicity of study subjects). Each 1-cm increase in hip circumference conferred a 22% increased odds of menarche. This association remained significant after controlling for demographic and anthropometric confounders. Total body fat mass was not associated with onset of menarche in this sample. Although these data suggest that gluteofemoral fat deposition predicts menarche, the ability to draw definitive conclusions about the timing of lower body fat deposition relative to the onset of menarche is limited by the cross-sectional nature of this study (21).

In contrast, it has been argued that differences in body habitus of prepubertal children do not vary significantly across race/ethnicity strata, but that anthropometric differences emerge during the pubertal transition and persist after puberty is completed (13, 22). Rather than focusing strictly on body habitus, several investigators have explored metabolic factors to explain racial/ethnic differences in pubertal timing.

Hyperinsulinism and reduced insulin sensitivity in prepubertal children have been implicated in racial/ethnic differences in pubertal timing (22). It has been suggested that prepubertal hyperinsulinemia stimulates hormone production from ovarian theca cells and perhaps from GnRH neurons initiating a cascade of earlier puberty in affected children (22, 24). Compared with whites, it has been reported that black girls have higher overall and basal insulin levels (25–30) that increase more robustly during puberty and decline less at its conclusion (25).

In support of the insulin theory of menarcheal timing, Casazza et al. (22) demonstrated that in addition to experiencing earlier menarche, black girls had significantly higher prepubertal fasting insulin and acute insulin responses to glucose infusion than did white girls. Although insulin sensitivity was significantly lower among blacks than whites, prepubertal BMI and total fat mass were comparable across race. Follicle-stimulating hormone concentrations were greater in blacks both before and during the pubertal transition. Estradiol levels were consistently higher in black children at each pubertal stage, although only significantly higher at Tanner stage I. A positive correlation between acute insulin response to glucose and estradiol was found in black girls, leading to the conclusion that postprandial insulin concentrations may stimulate estradiol and contribute to earlier menarche in black children (22).

Finally, there is growing evidence for a role of environmental exposures in the timing of puberty and in racial/ethnic differences in its onset. Human exposure to manufactured chemicals has increased dramatically in the 20th century. Nearly 80,000 compounds are presently registered for use in the United States, many with limited toxicity data. There is human data suggesting that exposure to endocrine-disrupting chemicals (EDCs) such as polybrominated

biphenyls, organochlorine pesticides, and polychlorinated biphenyls can induce pubertal changes (31–34). Animal data has implicated other EDCs such as bisphenol-A in early puberty as well (33, 34). Many of these chemicals can be found in common dietary sources, pesticides, and cosmetic products.

In summary, there is consistent data supporting a relationship between race/ethnicity and pubertal milestones. The data is strongest in support of the finding that puberty starts earliest for black children and latest for white children; Hispanic children appear to initiate puberty at a point intermediate to these groups. The current data on Asian children precludes a formal conclusion, but suggests they may start puberty later than other ethnic groups. Pubertal timing appears to be correlated with metabolic and anthropometric factors, but unraveling the precise nature of these relationships remains a matter of ongoing investigation. Environmental endocrine disruptors may also accelerate the timing puberty and contribute to a disparity if non-white children are more likely to be exposed to these chemicals than white children. These facts suggest that environmental correlates of race and ethnicity factor prominently in directing the earliest part of the reproductive spectrum. Based on family and twin studies, though, genetic regulation of puberty explains at least 50% of the variability seen in timing. This leaves open the possibility that genetic correlates of race and ethnicity may drive the variations in pubertal onset (35) either alone or through interactions with environmental factors.

ASSISTED REPRODUCTIVE TECHNOLOGY OUTCOMES

A growing number of studies have investigated the association between race/ethnicity and ART (in vitro fertilization and intacytoplasmic sperm injection) outcomes. Some have identified racial/ethnic differences (36–41), whereas others have not (42–45). Most of the existing literature has focused on comparisons between white and black women (36–38, 42, 43) with less data examining ART outcomes in Hispanics (40, 44) and Asians (39–41). In addition to the existence of variability in results in the literature, there is also some heterogeneity in study design and methodology that should be considered when interpreting existing studies.

Sharara and McClamrock (36) published the first U.S. study of racial determinants of ART outcomes, studying black and white women seeking care at a university-based program in an insurance mandated state (36). Women were excluded from analysis if they had specific anatomic correlates of poor outcome (hydrosalpinges and intracavitary lesions) or if they had biochemical evidence of compromised ovarian reserve (FSH of 11 IU/L or greater). Multiple cycles per women were studied. Compared with whites, black women were more likely to have a diagnosis of tubal factor infertility ($P<.001$), had higher mean BMI ($P=.038$), and were more likely to require microdose Lupron flare protocol during stimulation ($P=.012$). On average, black women had 1.3 more years of infertility before treatment than whites ($P=.016$). The groups were comparable by age, day 3 FSH levels, cycle cancellation rate, and multiple embryologic predictors of pregnancy (number of oocytes retrieved, number of embryos transferred). Black women experienced significantly lower implantation and clinical pregnancy rates per cycle than white women (implantation rate 9.8% in blacks vs. 23.4% in white women, $P=.0005$; clinical pregnancy rate 19.2% in blacks vs. 42.2% in white women, $P=.009$). The ongoing pregnancy rate per cycle (a pregnancy beyond 20 weeks gestation or a live birth) was also significantly lower in black than in white women (14.9% vs. 38.8%, $P=.005$) (36).

This study offers a compelling argument for the influence of race upon ART outcomes with the affect of race mediated in part by differences in BMI and duration of infertility. Unfortunately, these factors (and other potential confounders) are not controlled for in a formal way in the analysis, making it difficult to determine the strength of race as an independent predictor of ART treatments. Investigating outcomes in a state with an insurance mandate to cover infertility services is a stated strength of the study, as this would ostensibly reduce the impact of socioeconomic factors on ART outcomes. Indeed, in this report, 28% of the patients treated were black, significantly more than the reported proportion of black women receiving ART treatments nationwide (43). However, despite the presence of a mandate, there was still a racial disparity in the duration of infertility before ART was initiated suggesting relative underuse of ART treatments by black women. This difference confirms the growing literature showing that insurance mandates have not been able to completely bridge the racial gap in access to infertility services (46–48).

Feinberg et al. (43) addressed the issue of access and socioeconomic factors by comparing ART outcomes in black and white women military personnel. In this equal-access-to-care setting, 17.4% of the 1457 women studied were black: a fourfold increase in use compared with the U.S. ART population. Black and white women were comparable with respect to age, day 3 FSH levels, amount of gonadotropin administered during stimulation, peak estradiol levels, number of mature oocytes retrieved, and number of embryos transferred. However, black women were nearly three times more likely than white women to have leiomyoma as a stated cause of infertility (odds ratio [OR] 2.85, $P<.0001$) and nearly twice as likely to be diagnosed with tubal factor infertility (OR 1.91, $P<.0001$). In an analysis that adjusted for the presence of fibroids (an independent predictor of outcomes in this series), the association between race and ART outcomes (clinical pregnancy rates, spontaneous miscarriage rates, and live birth rates) was not significant (43).

The use of a very specialized population such as the military was a unique approach to control for the influence of limited healthcare access and other social factors on ART outcomes. A potential trade off for having studied such a unique population is the sacrifice of generalizability of findings to other groups of women. The investigators also acknowledge that sample size limitations may have hindered the ability to detect subtle differences in treatment outcomes by race (43).

It is possible that other investigations have also been limited by sample size constraints despite valid methodologic approaches. Of the four studies that found no association between race and ART outcomes the sample sizes ranged from 251 to 1,135 subjects, and none were as large as the Feinberg study, which showed no association (42–45). One of these studies, by Dayal et al. (42), has several strengths: race was self-identified using very strict criteria, and socioeconomic status was addressed by recruiting subjects from Washington DC, which has a disproportionately high middle-class black population compared with other regions of the country. Although differences in ART outcomes across race were not found, the sample size of the study ($n = 251$) was only sufficient to detect a 27% difference in pregnancy between groups. A clinically relevant, though small, difference could have missed detection in this sample. Furthermore, the live birth rate in the white subjects was somewhat lower than the SART national average for the period of time that this study was conducted (24% in the study population vs. 32% in SART data), whereas the live birth rate for blacks was comparable to SART data for live births (25% in study population vs. 22% in SART data) (49). This birth rate in whites combined with sample

size considerations could limit the ability to detect a difference if one existed (42, 49).

As this area of investigation has evolved, larger datasets have been examined permitting a more thorough evaluation of ART outcomes in multiple racial/ethnic groups including Asians and Hispanics. Specifically, studies using data from the national registry of ART cycles in the US. collected by the Society for Assisted Reproductive Technology and maintained by the Centers for Disease Control and Prevention, has circumvented issues of restricted sample size and potential type two errors. As these reports have relied on registry data, a unique set of limitations in the interpretation of results must be considered. Specific information regarding socioeconomic status and other potential confounders is not uniformly available. Racial categorization of patients is not standardized among clinics allowing for possible misclassification from center to center. The units of measure to determine treatment outcome must also be taken into consideration: registries track total number of cycles completed, which allows for individual patients to be represented in the dataset more than once. Women who choose to repeat cycles when previous attempts have failed may be different than women who stop trying in ways that relate both to the risk factor of interest (race/ethnicity) and the outcome (pregnancy). Investigators must recognize this potential for repeated-measure bias and aim to eliminate its influence from study findings whenever possible.

Four large database studies have recently noted consistent findings indicating racial/ethnic differences in ART outcomes (37–40). One of the first of these studies examined 80,390 nondonor cycles (both fresh and frozen) from SART for the years 1999 and 2000 (38). Additional inclusion criteria included cycles from clinics that performed at least 50 ART cycles annually and reported race >95% of the time. Of the 80,390 cycles evaluated, 3,666 were among black women (4.6%), 68,607 were among white women (85.4%), and 8,036 (11.9%) were among women of other races and ethnicities. Only outcomes in blacks and whites were compared.

In this series, black women had a greater duration of infertility before ART than white women (40 months vs. 34 months for those having their initial cycle and 48 vs. 36 months for women who had previously undergone ART [$P<.001$]). This translated to older mean ages for black women at treatment than for white women. When analyzing all cycles in the dataset, black women were less likely to experience a live birth per cycle of ART initiated compared with whites after controlling for, age, parity, diagnosis, and clinic factors. It was also noted that the overall live birth rate per fresh nondonor cycle for black women (18.7%) was below the lower 95% confidence interval (CI) for the rate among all races in the United States during 1999 to 2000. In contrast, the live birth rate among whites (26.3%) was above the 95% CI for all races nationally (p value for difference in live birth rates between blacks and whites, <.001). When restricting the analysis to patients receiving their first ART cycle, black women were 24% less likely to experience a live birth than whites when adjusting for the same confounders ($P<.001$). Black women who had been treated with ART previously were 38% percent less likely to have a live birth per cycle ($P<.001$). There were no racial differences in live birth when comparing frozen embryo transfer cycles (38).

In a follow-up study, Seifer et al. (37) investigated trends in ART outcomes in black and white women by comparing SART database outcomes for 2004 to 2006 with previously reported outcomes for 1999 to 2000. A total of 158,693 nondonor IVF cycles were analyzed. The proportion of cycles in which black women were treated for the first time increased from 5.4% in the 1999 to 2000 series to 8.4% in the 2004 to 2006 series ($P<.001$) as did the proportion of cycles for black women with previous ART cycles (4.6% to 7.1%, $P<.001$). However, trends in ART outcomes were summarily worse for black women over time, representing an expansion of the disparity demonstrated in the analysis of 1999 to 2000 SART data. This widening of the gap in treatment outcomes may be explained in part by worsening of prognostic indicators in black women over time. The proportion of black women undergoing ART for the first time who were over 35 years old increased in the 2004 to 2006 assessment (57.9%) compared with the 1999 to 2000 assessment (49.9%) ($P<.001$). In addition, the proportion of black women treated for the first time with the diagnosis of diminished ovarian reserve nearly doubled between these time points (7.5% in 1999–2000 vs. 14.4% in 2004–2006, $P<.001$). Significant upward trends were also noted in the diagnosis of unexplained infertility and uterine factors in black patients ($P<.0001$) (37).

In accordance with these trends was a plateau in the likelihood of clinical pregnancy and live birth per cycle of ART in black women. The live birth rate per cycle initiated in black women (first cycle of ART) in 1999 to 2000 was 20.7% compared with 22.2% in 2004 to 2006 ($P=.19$). This trend contrasted sharply with outcomes in white women who demonstrated improvements in both clinical pregnancy (first cycle ART clinical pregnancy rate/cycle of 33.6% in 1999–2000 vs. 38.3% in 2004–2006, $P<.001$) and live birth rate over time (first cycle ART live birth rate/cycle 28.4% in 1999–2000 vs. 32.3% in 2004–2006). In the 2004–2006 assessment, black women treated for the first time were 31% less likely to achieve a live birth than white women (adjusted relative risk 1.31, 95% CI 1.26–1.37). Compared to the adjusted relative risk of first cycle treatment failure for blacks compared to whites descries in the 1999–2000 series (1.24) this updated result represents a significant downard trend. Black women who had ever had prior ART treatment were 33% less likely than whites to achieve a live birth ($P<.001$), which was comparable to the risk in the 1999 to 2000 assessment (adjusted relative risk 1.38). Finally, a 10% lower adjusted odds of live birth after transfer of cryopreserved embryos was noted in black women compared with white women. This finding was not demonstrated in the analysis of 1999 to 2000 cycle data (37). This analysis raises concern of a growing disparity in ART outcomes over time.

Additional studies have used SART to investigate disparities in ART outcomes expanding on the racial/ethnic groups studied to include Asian and Hispanic women. Purcell et al. (39) performed a parallel analysis in Asian women compared with whites using cycles from SART (1999–2000) and from the University of California San Francisco. A total of 27,272 cycles from SART were studied, of which 1429 (5.2%) were in Asian women. Cycles from SART included first-cycle, fresh, nondonor ART treatments. Of the cycles studied from the University of California San Francisco (567 total cycles) 197 were performed in Asian women (34.74%). In both data sets, Asian women had lower odds of clinical pregnancy and live birth than white women. Multivariate logistic regression using the SART registry data demonstrated that Asian women were 24% less likely to achieve a live birth after ART (OR 0.76, 95% CI 0.66–0.88). The clinic-specific data confirmed this disparity with comparably diminished odds of pregnancy in Asian patients compared with whites (OR 0.59, 95% CI 0.37–0.94) (39).

Fujimoto et al. (40) have published the largest evaluation to date of ART outcomes in multiple racial/ethnic groups based on

SART registry data. A total of 139,027 nondonor ART cycles between 2004 and 2006 were assessed. Outcomes were compared between white, black, Asian, and Hispanic women. Compared with the referent group of white women, all other groups had lower live birth rates adjusting for maternal age, number of embryos transferred, and infertility diagnosis ($P<.0001$). Asian women, who comprised 9.8% of the cycles evaluated (13,671), had at 14% lower odds of clinical pregnancy than whites and a 10% lower odds of having a live birth after ART. Hispanic women (8,969 cycles, 6.5% of total cycle number) had clinical pregnancy rates comparable to whites but were 13% less likely to have a live birth after ART. Black women (8,903 cycles 6.5% of total cycle number) also had similar clinical pregnancy rates as white women but were 38% less likely to achieve a live birth. All ethnic groups studied had significantly higher miscarriage/stillbirth rates than white women ($P<.0001$) (40).

Perinatal morbidity was also significantly increased in the pregnancies of all ethnic minority groups compared with white women (40). Among singleton pregnancies, there was a significantly higher likelihood of moderate and severe growth restriction in all ethnic groups compared with whites. Singleton pregnancies of black and Hispanic mothers were more likely to be affected by preterm birth than whites; Asian women did not have an increased risk of preterm delivery of singleton conceptions. In twin gestations, black women had the highest overall odds of preterm delivery (OR 1.64, 95% CI 1.29–2.08) and of having twins affected with moderate and severe growth restriction. Hispanic women had increased odds of delivering very preterm twins ($\leq$29 weeks, OR 1.36, 95% CI 1.01–1.82), but overall, did not have a significantly higher risk of delivering twins preterm compared with whites (OR 1.14, 95% CI 0.95–1.37) (40).

Despite the acknowledged limitations of these large studies, there is a consistent finding of race/ethnicity as a risk factor for poor ART outcomes after adjusting for many confounders. The impact of race/ethnicity on accessibility to ART centers requires additional study. Such research is needed to better understand if race/ethnicity reflects genetic factors that may influence ART outcomes or if these categories are proxies for socioeconomic status, environmental influences, or behavioral differences that contribute to outcomes. It is likely that some combination of these factors is responsible for the disparities that have been demonstrated.

REPRODUCTIVE AGING

There is a growing body of research indicating that reproductive aging may be influenced by race and ethnicity. We choose to look at three facets of the literature to explore this possibility in more depth: menopausal timing, hormonal markers, and perimenopausal symptoms.

Menopausal Timing

Several reports have suggested an association between race/ethnicity and timing of natural menopausal (50–53), whereas others have not supported this conclusion (54). Bromberg et al. (51) conducted a prospective study of the association between demographic, stress-related, and behavioral factors and age at natural menopause. Despite comprising only 10% of the study sample, black women demonstrated a significantly lower median age at menopause (49.3 years) than whites (51.2 years, $P<.05$). Of note, life stress (assessed by a validated instrument) significantly modified the effect of race on menopausal timing. The median age of menopause in black women with significant life stress was 48.4 years; blacks without significant life stress entered the menopause at age 49.9 years ($P<.006$). After controlling for multiple demographic and reproductive confounders, time to natural menopause in relation to age at study entry was over four times faster in blacks than in whites (51). In this series, race was a stronger risk factor for earlier time to menopause than was smoking, a well-known reproductive toxicant associated early menopause (51).

Investigators from the Study of Women Across the Nation (SWAN), a racially diverse, multicenter, prospective study of the natural history of the menopausal transition, have reported on multiple factors associated with age at natural menopause, including race and ethnicity. In this cross-sectional study of nearly 15,000 women, menopausal age was comparable in whites, Hispanics, blacks, and Chinese women; Japanese women experienced menopause several months later than white women (53). This finding contrasts with reports that have described earlier or comparable menopause in various Asian populations compared with white women in the United States and Europe (55–59). Of note, many of the studies of menopausal timing in Asian populations have either been descriptive without a concurrent comparison group or have suboptimally adjusted for confounding (55–59). Several studies evaluating onset of menopause in Hispanic populations in Mexico and South America have described menopause ranging from 45 to 48.2 years, but methodologic issues may have biased some these estimates to lower ages (60–62).

In a separate study from SWAN, the prevalence of premature ovarian failure (cessation of menses before age 40) across several ethnic groups was investigated. In a cross-sectional survey of 11,652 women, the prevalence of premature ovarian failure (POF) was significantly different according to race/ethnicity ($P=.01$) (63). Premature ovarian failure was more prevalent in blacks (1.4%, 40/2814) and Hispanics (1.4%, 21/1,456) than in whites (1.0%, 61/6,063); it was less common in Chinese women (0.5%, 3/592) and Japanese women 0.14%, 1/727). The prevalence of POF was not significantly different between Chinese and Japanese women. In addition, blacks (3.7%, 104/2,318,) and Hispanics (4.1%, 60/1,456) were more likely to enter menopause before age 45 than were whites (2.9%, 177/6,063). Menopause before the age of 45 was less common in Chinese (2.2%, 13/592) and Japanese women (0.8%, 6/644). The low prevalence of early menopause in Japanese women in this report is consistent with longitudinal data from the SWAN study in which menopause occurred somewhat later for Japanese women than for other groups studied (53). Additional conclusions about variables related to race and preceding the onset of POF could not be drawn given the cross-sectional nature of this study (63).

Finally, a report from NHANES III evaluated menopausal stage and FSH concentrations in a cross-section of over 1,600 black, white, and Hispanic women. In a multivariate regression model, Hispanic ethnicity was not a significant risk factor for hormonally defined menopause (FSH $>$20 IU/L). Black women had somewhat higher adjusted odds of elevated FSH levels and of postmenopausal status by menstrual patterns, but neither estimate was statistically significant (OR for elevated FSH concentration 1.3, 95% CI 0.9–1.8, OR for postmenopausal status 1.6, 95% CI 0.9–2.9). Hispanic women were more likely to be perimenopausal by menstrual patterns (OR 2.4, 95% CI 1.2–4.8) but not postmenopausal (54).

Hormonal Fluctuations

Prospective investigations of menopausal symptoms and reproductive hormones have elaborated an understanding of racial influences on the menopausal transition. Data from two ongoing investigations

have made significant contributions in this area: the Penn Ovarian Aging study and the SWAN study. Reports from both have shown associations between race and specific reproductive hormones in the years leading up to the menopause. The SWAN study investigators performed a cross-sectional analysis of hormones in white, black, Hispanic, Chinese, and Japanese women. The mean age of subjects reported on was 46.34 years, and 54.3% were premenopausal. In an analysis that adjusted for menopausal status, study site, day of the menstrual cycle, BMI, age, smoking, and alcohol consumption, the following conclusions were drawn: [1] mean serum FSH levels were significantly higher in black and Hispanic women than in other ethnic groups, [2] mean serum estradiol levels were not significantly different by race/ethnicity, and [3] BMI was significantly correlated with reproductive hormone levels in the perimenopause in all ethnic groups; specifically, BMI was negatively correlated with FSH and estradiol concentrations (64). In the unadjusted analysis of race/ethnicity and its association with hormone levels, Chinese women were noted to have significantly lower estradiol levels compared with all other groups studied (64). Although this relationship was attenuated and became nonsignificant in a multivariate regression model, estradiol concentrations were still 13% lower in Chinese women, a finding that has been demonstrated by other investigators (55, 65–69). Lower estradiol levels in pre- and perimenopausal Chinese women that decline less markedly during the menopausal transition have been proposed as an explanation for diminished reporting of menopausal symptoms in this group (64, 70).

Similar cross-sectional analyses of have been performed within the Penn Ovarian Aging cohort, a prospective study of hormonal changes and symptoms during the menopausal transition in black and white women (71, 72). The mean age of subjects in the most recent hormonal assessment was 45.7 years (range = 39–53 years) and 47% of the cohort was premenopausal (71). In reports from this study describing hormonal patterns, unadjusted levels of estradiol and LH were significantly lower in blacks than whites. No differences in FSH concentrations were found (71, 72). An adjusted analysis involving interactions between race, BMI, and menopausal status demonstrated that black premenopausal/perimenopausal women generally had lower estradiol levels than whites, especially at higher BMIs (P=.001) (71, 72).

The relationship between race and inhibin-B levels during the menopausal transition has also been investigated in the Penn Ovarian Aging cohort. In an analysis adjusted for BMI, menopausal stage, smoking, and additional pertinent covariates, black women demonstrated lower levels of inhibin-B than whites, but this difference was not statistically significant (P=.084) (73). Furthermore, there were no significant interactions between race and BMI or between race and menopausal stage in predicting inhibin-B levels in this population.

Anti-Mullerian hormone (AMH) has recently been identified as a highly sensitive marker of ovarian reserve. It is primarily produced by the pool of early-growing preantral and antral follicles, which are believed to serve as a proxy for the number of primordial follicles in the ovary (74, 75). It has been suggested that AMH may be the most accurate biomarker of ovarian aging and offer several advantages of traditional biomarkers of ovarian reserve (74, 76–79). Compared with other hormonal markers of reproductive aging, AMH begins to gradually decline earlier in life (74, 76–79), and levels are not influenced by pregnancy, hormonal contraceptives, or menstrual cycle timing (74, 79–84).

An extensive body of literature has demonstrated an inverse relationship between AMH and age but have inadequately controlled for race (76–78). Seifer et al. (85) analyzed changes in AMH in a racially diverse, multicenter cohort study of HIV-infected women and high-risk seronegative women enrolled in the Women's Interagency HIV Study. Anti-Mullerian hormone levels were assessed at two time points in the study (median age 37.5 years and 43.3 years). Black and Hispanic women were noted to have a somewhat greater likelihood of an undetectable AMH at the second assessment compared with whites (P=.09). In a repeated-measures linear regression model controlling for age, BMI, smoking, and HIV status, black women demonstrated average AMH values that were 25.2% lower than those in whites (P=.037) (85). Anti-Mullerian hormone levels in Hispanic women were 24.6% lower than white women in the adjusted analysis, but this difference did not reach statistical significance (P=.063). Of note, HIV infection status was not significantly associated with AMH values in the multivariate regression (85).

The data from the Interagency HIV study support a potential relationship between race and decline in AMH over time but contrast with results from the Penn Ovarian Aging Study. A subset of the Penn Ovarian Aging cohort was compared by AMH levels at a single time point. The mean age of the 122 women studied was 45.8 years, 52% were premenopausal, 27% were in the transition, and 21% were postmenopausal. In both univariate and adjusted analyses, black and white women had comparable AMH levels (86). In comparing the results of these studies, the mean age difference in the samples must be taken into account. A significant proportion of the Penn Ovarian Aging cohort was perimenopausal or postmenopausal and likely had undetectable AMH levels.

Perimenopausal Symptoms

Black race has been a reproducible and independent risk factor for the occurrence of hot flashes and other menopausal symptoms in women in the late reproductive years (87–90). In an early report from the Penn Ovarian Aging cohort, black women had a nearly twofold increased risk of experiencing hot flashes compared with white women (adjusted OR 1.9, P<.001, adjusted for BMI, smoking, education, reproductive history, depression, and alcohol) (87). Most of the women studied in this report were premenopausal (67%) and young (mean age 42.3 years). Additional reports from this cohort expanded on this association and have confirmed that black race is an independent predictor of vasomotor symptoms, vaginal dryness, and musculoskeletal complaints in advancing menopausal stages (88, 89).

These findings have been corroborated by results from the SWAN cohort (70, 90). In a recent report from this investigation, black women had a 1.6-fold increased risk of experiencing vasomotor symptoms during the menopausal transition (adjusted for BMI, smoking, menopausal stage, and anxiety symptoms) (90). In further adjusted analyses from this cohort, the following significant patterns emerged: Asian women (Chinese and Japanese) complained of the fewest vasomotor symptoms and the fewest menopausal symptoms overall; black women complained of more vasomotor symptoms, insomnia, musculoskeletal complaints, and vaginal dryness than whites but had fewer urinary symptoms; Hispanic women were comparable to white women with respect to vasomotor symptoms but had more urinary symptoms, vaginal dryness, palpitations, and forgetfulness (70).

The diminished frequency of vasomotor symptoms in Asian women in this report is consistent with other studies that have described less frequent vasomotor symptoms in Asian women than in women of European descent (59, 67–68). Most of the

literature describing the prevalence of vasomotor symptoms in perimenopausal Asian women has surveyed women in Asia rather than the United States and compared frequencies to historic controls of white women (59, 67–68). It has been suggested that there may be cultural differences in characterization of menopause by Asian women and difficulties translating terms relating to perimenopausal symptoms (68). It is possible that these differences may be less pronounced in Asian American women than in Asian women who have not immigrated to the United States. The SWAN investigators adjusted for language as a measure of acculturation when surveying women of Asian descent as a means of controlling for descriptive barriers in capturing symptoms appropriately (70).

While race appears to have a significant impact on symptom severity during reproductive aging; black women appear to rely less heavily on hormonal therapies for symptom management than whites (87). In addition, their response to hormone replacement may be attenuated compared with whites. A recent report of a subset of women from the Women's Health Initiative who had undergone hysterectomy and had symptoms at baseline demonstrated that estrogen replacement effectively treated hot flashes in 56% black women compared with 80% of whites ($P<.001$). This difference accounted for BMI, smoking status, and previous hormone use (91).

In summary, there is growing evidence that the late stages of reproductive aging have racial and ethnic influences. Strong evidence from multiple, racially diverse, prospective studies have confirmed that race and ethnicity are independently associated with vasomotor symptoms during the menopausal transition. The effect of race/ethnicity on reproductive hormones in the approach to the menopause appears to be significant but variable in different reports. Adequate control of confounding and rigorous investigation of interactions is critical to properly understanding the true relationship between race and menopausal endpoints. Ultimately, additional follow-up of prospective aging cohorts is needed to solidify the associations between race, hormones, and symptoms, and to determine how these factors coalesce to predict menopausal onset.

DISCUSSION

We have reviewed and summarized the available literature examining differences in reproductive potential in black, Hispanic, Asian, and white women (Table 1). Onset of puberty, outcomes following ART treatment and the menopausal transition each represent women along a natural continuum of the reproductive life cycle. Each stage is sensitive to genetic and environmental influences that may correlate with race and ethnicity. The ultimate goal of identifying racial disparities in reproduction is to isolate the basic determinants of disparities and formulate strategies to improve outcomes for women at risk.

Early puberty, for instance, has been associated with obesity in adolescence and adulthood (14, 92–94). Obesity is a growing public health concern associated with significant morbidity in children and adults. Earlier puberty, as has been demonstrated in black and Hispanic children, may contribute to the discrepant prevalence of obesity in these populations (14, 92, 93–96). Early puberty may also reflect early life nutritional, and environmental factors that increase future risk of metabolic disease certain racial and ethnic groups.

Our review of the literature provides evidence supporting racial and ethnic disparities in the odds of pregnancy in infertile women treated with ART. Data from various sources was reviewed including observational studies with modest to intermediate samples sizes (42–44) and reports of thousands of cycles from the SART registry (37–40). Many of the smaller studies did not show an association between race/ethnicity and ART outcomes (42–44), whereas the studies based on SART data unequivocally did (37–40). A critique of many of the negative reports concern sample size and possible type II errors. The reports using SART data address this drawback, but must be interpreted in light of the inability to control for socioeconomic status and possible inconsistencies in the categorization of race and ethnicity in various clinics. When many of the non-SART reports addressed socioeconomic status in their analysis, associations between race/ethnicity and ART were not significant. Thus, although the relationship between race/ethnicity and ART outcomes appears to represent a disparity based on reports from large datasets, it is possible that the association is attenuated by the effect of socioeconomic status. As concerns the appropriateness of race and ethnic strata in SART, patients are categorized as black, white, Asian or Hispanic. The US Census Bureau recommends considering race and ethnicity as separate and distinct entities (97, 98). Using this approach, respondents should characterize their race (white, black, Asian, Indian/Alaska native, native Hawaiian/Pacific Islander, or other) and then their ethnicity (Hispanic/Latino or non-Hispanic/non-Latino). Misclassification bias could be introduced by not considering race and ethnicity separately.

The phenomenon of ART disparities parallels evidence from the National Survey of Family Growth reporting differences in prevalence of infertility in black and Hispanic married women over the previous 20 years. In a multivariate analysis of data from the survey, black women were 80% more likely to report infertility in the previous 12 months than white women; Hispanic women had a 30% higher odds of infertility than whites (99). The decline in infertility in the overall National Survey of Family Growth sample between 1982 and 2002 (from 8.5% to 7.4%) contrasted significantly with the increase in infertility prevalence among black women (from 7.1% to 11.6%) over that same period. The prevalence of infertility remained stable for Hispanic women (7.2% in 1982 and 7.7% in 2002) (99). Two potential explanations for these findings include disparate environmental exposures and diminished access to infertility treatments across racial and ethnic groups. Diminished use of infertility treatments in black women (46–48) compared with whites is a proven barrier to optimal ART outcomes (37, 38), but a solution to eliminating this barrier is not apparent. It has been demonstrated that in equal access settings such as the military, use of ART in black women is high (43); however, even in states with an insurance mandate to cover most or all of the costs of ART, use in black women still lags that of whites (36, 46–48). Furthermore, when Seifer et al. (38) controlled for age and duration of infertility, disparities in live birth rates after treatment persisted. This would suggest that in addition to improving access to care, other correlates of race and ethnicity that affect ART outcomes must be isolated and addressed.

Several conclusions about racial/ethnic differences in reproductive aging can be drawn from the current literature but several questions remain. Menopausal symptom reporting varies by race/ethnicity which likely has both hormonal and sociocultural correlates. During the menopausal transition, black women have significantly diminished quality of life compared with whites, and do not appear to get sufficient symptom relief from first line hormonal therapies (91). Recent experience with treating menopausal symptoms has shifted the paradigm to individualization of care. Understanding the unique ways that women age reproductively is in line with this

TABLE 1

Summary of differences in reproductive endpoints across racial/ethnic groups.

Outcome	Summary of findings	Strengths and weakness of evidence
Pubertal timing	Timing of pubertal milestones earliest in black children followed by Hispanic children then white children (9, 10) Asian children may have later menarche than whites (16, 17)	Best data describing earlier menarche in blacks and Hispanics comes from studies with large samples with thousands of children (9, 10) Most studies are cross-sectional and rely on recall of subjects to time events in the past (9, 10). Paucity of data on Asian children describing pubertal timing (16, 17)
ART treatment outcomes	Four large studies using SART data have consistently shown diminished live birth rates in racial/ethnic groups compared with whites (37–40) Several other studies with smaller samples have not consistently shown an association between race/ethnicity and assisted reproduction technologies (ART) outcome (42, 43, 45). Increased perinatal morbidity in ART-conceived pregnancies in racial/ethnic minorities (40)	Registry data has large numbers of subjects and can control for some confounders (37-40) Registry data cannot reliably access individual level data, racial categorizations are not standardized, and cannot control for some important confounders (body mass index [BMI], socioeconomic status [SES]) (37–40) Smaller studies may be underpowered to show subtle differences in outcomes associated with race/ethnicity (42, 43, 45)
Reproductive aging	Timing of menopause may differ between ethnic groups with somewhat earlier onset in blacks and somewhat later onset in Japanese (51, 53) Several biomarkers of aging appear to differ by race/ethnicity compared with whites: • Lower anti-Mullerian hormone (AMH) levels in blacks and Hispanics (85) • Lower estradiol levels in blacks (71, 72) • Higher FSH levels in blacks (64) • Lower estradiol levels in Chinese women (borderline significance) (64) • Menopausal symptoms occur with greater frequency in blacks compared with whites (87–89) • Menopausal symptoms occur with lower frequency in Asians than whites (59, 67, 68, 70)	Data regarding differences in onset of menopause across race/ethnicity still accumulating from large prospective studies BMI often interacts with race/ethnicity to influence hormones but existing data still supports independent effects of race (64, 71)

Butts. Racial/ethnic differences in reproductive potential across the life cycle. Fertil Steril 2010.

approach, and could improve the delivery of menopausal care to a diverse population.

The fundamental question of whether racial and ethnic minorities are at higher risk for early menopause remains a matter of inquiry. We have presented data showing racial/ethnic differences in the prevalence of premature ovarian failure (63), and one report of black women entering menopause approximately 2 years earlier than whites (51). Although higher FSH (71, 72) and lower AMH (85) levels have been demonstrated in reproductively aging black women compared with whites, the results of ongoing longitudinal studies of large populations will need to be analyzed to draw more firm conclusions about racial/ethnic disparities in menopausal timing.

The review of these data reveal many provocative findings while raising unresolved questions. How can all these data be synthesized into a unifying theory of the impact of race and ethnicity on major milestones across the reproductive life span of women? What potentially modifiable correlates of race and ethnicity can be identified to help optimize reproductive outcomes for women? We propose that there may be environmental exposures and risk factors common to discrete populations of women that impact pubertal timing, infertility, and menopause. Obesity, for instance, impacts each of the reproductive milestones studied herein, and black and Hispanic women are more likely to be effected by obesity than whites (95, 96). Obesity, either alone or in combination with insulin dysregulation, appears to effect earlier pubertal onset; in addition, early puberty likely enhances the odds of persistent obesity later in life (14, 92–94). Obesity is a risk factor for miscarriage both in the general population and after ART treatment (100–102). Obesity also has an impact on reproductive hormones in the perimenopause (64, 71–73) and increases the likelihood of vasomotor symptoms (87–89).

There is insufficient evidence to suggest that pubertal timing affects odds of infertility or menopausal age. Studies of risk factors for menopausal timing have not consistently suggested a role for early age at menarche and age at menopause; however, many of these reports have not included diverse populations of women (54). It is possible that timing of menarche may be associated with menopausal timing in certain racial and ethnic groups, as has been suggested by some reports (55). The precise mechanism of how early menarche, for instance, might increase the risk for early menopause has not been elucidated.

The link between infertility and later reproductive aging may be more direct and significant than between menarche and menopause.

The association between race/ethnicity and failure to conceive with IVF could reflect subtle differences in reproductive aging that foreshadow a faster trajectory of ovarian aging later in life.

If race/ethnicity is a risk factor for subtle changes in ovarian reserve reflected in ART outcomes, it will be important for clinicians to acknowledge and address this fact. It will also be critical to unravel the factors common to both ART outcomes and later aging so that they may be appropriately addressed. Whether the time course of the reproductive axis is influenced differently as a function of race by genetic or environmental factors will require much further investigation. Going forward, the continued assessment of race as a predictor of reproductive outcomes is needed; appropriately executed, longitudinal investigations will shed the most light on our understanding of the extent of differences across racial strata.

REFERENCES

1. U.S. Department of Health and Human Services: Office of Disease Prevention and Health Promotion—Healthy People 2010. Nasnewsletter 2000;15:3.
2. Davidson EC Jr, Fukushima T. The racial disparity in infant mortality. N Engl J Med 1992;327:1022–4.
3. Frisbie WP, Song SE, Powers DA, Street JA. The increasing racial disparity in infant mortality: respiratory distress syndrome and other causes. Demography 2004;41:773–800.
4. Kelley E, Moy E, Dayton E. Health care quality and disparities: lessons from the first national reports. Med Care 2005;43:I1–2.
5. Williams DR. Race and health: basic questions, emerging directions. Ann Epidemiol 1997;7:322–33.
6. Williams DR, Rucker TD. Understanding and addressing racial disparities in health care. Health Care Financ Rev 2000;21:75–90.
7. Rebbeck TR, Halbert CH, Sankar P. Genetics, epidemiology, and cancer disparities: is it black and white? J Clin Oncol 2006;24:2164–9.
8. Rebbeck TR, Sankar P. Ethnicity, ancestry, and race in molecular epidemiologic research. Cancer Epidemiol Biomarkers Prev 2005;14:2467–71.
9. Wu T, Mendola P, Buck GM. Ethnic differences in the presence of secondary sex characteristics and menarche among US girls: the Third National Health and Nutrition Examination Survey, 1988–1994. Pediatrics 2002;110:752–7.
10. Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics 1997;99:505–12.
11. Chumlea WC, Schubert CM, Roche AF, Kulin HE, Lee PA, Himes JH, et al. Age at menarche and racial comparisons in US girls. Pediatrics 2003;111:110–3.
12. Kaplowitz P. Pubertal development in girls: secular trends. Curr Opin Obstet Gynecol 2006;18:487–91.
13. Kimm SY, Barton BA, Obarzanek E, McMahon RP, Sabry ZI, Waclawiw MA, et al. Racial divergence in adiposity during adolescence: The NHLBI Growth and Health Study. Pediatrics 2001;107:E34.
14. Slyper AH. The pubertal timing controversy in the USA, and a review of possible causative factors for the advance in timing of onset of puberty. Clin Endocrinol (Oxf) 2006;65:1–8.
15. Koprowski C, Ross RK, Mack WJ, Henderson BE, Bernstein L. Diet, body size and menarche in a multiethnic cohort. Br J Cancer 1999;79:1907–11.
16. Weaver CM, McCabe LD, McCabe GP, Novotny R, Van Loan M, Going S, et al. Bone mineral and predictors of bone mass in white, Hispanic, and Asian early pubertal girls. Calcif Tissue Int 2007;81:352–63.
17. Novotny R, Going S, Teegarden D, Vam Loan M, McCabe G, McCabe L, et al. Hispanic and Asian pubertal girls have higher android/gynoid fat ratio than whites. Obesity (Silver Spring) 2007;15:1565–70.
18. 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;40:227–31.
19. Frisch RE, McArthur JW. Menstrual cycles: fatness as a determinant of minimum weight for height necessary for their maintenance or onset. Science 1974;185:949–51.
20. Maclure M, Travis LB, Willett W, MacMahon B. A prospective cohort study of nutrient intake and age at menarche. Am J Clin Nutr 1991;54:649–56.
21. Lassek WD, Gaulin SJ. Brief communication: menarche is related to fat distribution. Am J Phys Anthropol 2007;133:1147–51.
22. Casazza K, Goran MI, Gower BA. Associations among insulin, estrogen, and fat mass gain over the pubertal transition in African-American and European-American girls. J Clin Endocrinol Metab 2008;93:2610–5.
23. He Q, Horlick M, Thornton J, Wang J, Pierson RN Jr, HesHkla S, et al. Sex and race differences in fat distribution among Asian, African-American, and Caucasian prepubertal children. J Clin Endocrinol Metab 2002;87:2164–70.
24. Poretsky L, Cataldo NA, Rosenwaks Z, Giudice LC. The insulin-related ovarian regulatory system in health and disease. Endocr Rev 1999;20:535–82.
25. Klein DJ, Aronson Friedman L, Harlan WR, Barton BA, Schreiber GB, Cohen RM, et al. Obesity and the development of insulin resistance and impaired fasting glucose in black and white adolescent girls: a longitudinal study. Diabetes Care 2004;27:378–83.
26. Arslanian S. Insulin secretion and sensitivity in healthy African-American vs. American white children. Clin Pediatr (Phila) 1998;37:81–8.
27. Gower BA, Fernandez JR, Beasley TM, Shriver MD, Goran MI. Using genetic admixture to explain racial differences in insulin-related phenotypes. Diabetes 2003;52:1047–51.
28. Goran MI, Gower BA. Longitudinal study on pubertal insulin resistance. Diabetes 2001;50:2444–50.
29. Gower BA, Nagy TR, Goran MI. Visceral fat, insulin sensitivity, and lipids in prepubertal children. Diabetes 1999;48:1515–21.
30. Gower BA, Nagy TR, Trowbridge CA, Dezenberg C, Goran MI. Fat distribution and insulin response in prepubertal African American and white children. Am J Clin Nutr 1998;67:821–7.
31. Blanck HM, Marcus M, Tolbert PE, Rubin C, Alden CK, Hertzberg VS, et al. Age at menarche and tanner stage in girls exposed in utero and postnatally to polybrominated biphenyl. Epidemiology 2000;11:641–7.
32. Wolff MS, Landrigan PJ. Organochlorine chemicals and children's health. J Pediatr 2002;140:10–3.
33. McKinney JD, Waller CL. Polychlorinated biphenyls as hormonally active structural analogues. Environ Health Perspect 1994;102:290–7.
34. Crain DA, Janssen SJ, Edwards TM, Heindel J, Ho SM, Hunt P, et al. Female reproductive disorders: the roles of endocrine-disrupting compounds and developmental timing. Fertil Steril 2008;90:911–40.
35. Palmert MR, Boepple PA. Variation in the timing of puberty: clinical spectrum and genetic investigation. J Clin Endocrinol Metab 2001;86:2364–8.
36. Sharara FI, McClamrock HD. Differences in in vitro fertilization (IVF) outcome between white and black women in an inner-city, university-based IVF program. Fertil Steril 2000;73:1170–3.
37. Seifer DB, Zackula R, Grainger DA. Trends of racial disparities in assisted reproductive technology outcomes in black women compared with white women: Society for Assisted Reproductive Technology 1999 and 2000 vs. 2004–2006. Fertil Steril April 14, 2009 [Epub ahead of print].
38. Seifer DB, Frazier LM, Grainger DA. Disparity in assisted reproductive technologies outcomes in black women compared with white women. Fertil Steril 2008;90:1701–10.
39. Purcell K, Schembri M, Frazier LM, Rall MJ, Shen S, Croughan M, et al. Asian ethnicity is associated with reduced pregnancy outcomes after assisted reproductive technology. Fertil Steril 2007;87:297–302.
40. Fujimoto VY, Luke B, Brown MB, Jain T, Armstrong A, Grainger DA, et al. Racial and ethnic disparities in assisted reproductive technology outcomes in the United States. Fertil Steril December 10, 2008 [Epub ahead of print].
41. Palep-Singh M, Picton HM, Vrotsou K, Maruthini D, Balen AH. South Asian women with polycystic ovary syndrome exhibit greater sensitivity to gonadotropin stimulation with reduced fertilization and ongoing pregnancy rates than their Caucasian counterparts. Eur J Obstet Gynecol Reprod Biol 2007;134:202–7.
42. Dayal MB, Gindoff P, Dubey A, Spitzer TL, Bergin A, Peak D, et al. Does ethnicity influence in vitro fertilization (IVF) birth outcomes? Fertil Steril 2009;91:2414–8.
43. Feinberg EC, Larsen FW, Catherino WH, Zhang J, Armstrong AY. Comparison of assisted reproductive technology utilization and outcomes between Caucasian and African American patients in an equal-access-to-care setting. Fertil Steril 2006;85:888–94.
44. Bendikson K, Cramer DW, Vitonis A, Hornstein MD. Ethnic background and in vitro fertilization outcomes. Int J Gynaecol Obstet 2005;88:342–6.
45. Matalliotakis I, Cakmak H, Arici A, Goumenou A, Fragouli Y, Sakkas D. Epidemiological factors influencing IVF outcome: evidence from the Yale IVF program. J Obstet Gynaecol 2008;28:204–8.
46. Jain T, Hornstein MD. Disparities in access to infertility services in a state with mandated insurance coverage. Fertil Steril 2005;84:221–3.
47. Jain T. Socioeconomic and racial disparities among infertility patients seeking care. Fertil Steril 2006;85:876–81.
48. Bitler M, Schmidt L. Health disparities and infertility: impacts of state-level insurance mandates. Fertil Steril 2006;85:858–65.
49. Centers for Disease Control and Prevention Assisted Reproductive Technology Report. 2004.

50. Stanford JL, Hartge P, Brinton LA, Hoover RN, Brookmeyer R. Factors influencing the age at natural menopause. J Chronic Dis 1987;40:995–1002.
51. Bromberger JT, Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Prospective study of the determinants of age at menopause. Am J Epidemiol 1997;145:124–33.
52. MacMahon B, Worcester J. Age at menopause. United States—1960–1962. Vital Health Stat 1966;11:1–20.
53. Gold EB, Bromberger J, Crawford S, Samuels S, Greendale GA, Harlow DS, et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. Am J Epidemiol 2001;153:865–74.
54. Cooper GS, Baird DD, Darden FR. Measures of menopausal status in relation to demographic, reproductive, and behavioral characteristics in a population-based study of women aged 35–49 years. Am J Epidemiol 2001;153:1159–65.
55. Boulet MJ, Oddens BJ, Lehert P, Vemer HM, Visser A. Climacteric and menopause in seven South-east Asian countries. Maturitas 1994;19:157–76.
56. Tamada T, Iwasaki H. [Age at natural menopause in Japanese women]. Nippon Sanka Fujinka Gakkai Zasshi 1995;47:947–52.
57. Ismael NN. A study on the menopause in Malaysia. Maturitas 1994;19:205–9.
58. Chompootweep S, Tankeyoon M, Yamarat K, Poomsuwan P, Dusitsin N. The menopausal age and climacteric complaints in Thai women in Bangkok. Maturitas 1993;17:63–71.
59. Ramoso-Jalbuena J. Climacteric Filipino women: a preliminary survey in the Philippines. Maturitas 1994;19:183–90.
60. Garrido-Latorre F, Lazcano-Ponce EC, Lopez-Carrillo L, Hernandez-Avila M. Age of natural menopause among women in Mexico City. Int J Gynaecol Obstet 1996;53:159–66.
61. Gonzales GF, Villena A, De La Cruz D. Age of natural menopause among women in Lima City, Peru. Int J Gynaecol Obstet 1997;57:69–72.
62. Beyene Y. Cultural significance and physiological manifestations of menopause. A biocultural analysis. Cult Med Psychiatry 1986;10:47–71.
63. Luborsky JL, Meyer P, Sowers MF, Gold EB, Santoro N. Premature menopause in a multi-ethnic population study of the menopause transition. Hum Reprod 2003;18:199–206.
64. Randolph JF Jr, Sowers M, Gold EB, Mohr BA, Luborsky L, Santoro N, et al. Reproductive hormones in the early menopausal transition: relationship to ethnicity, body size, and menopausal status. J Clin Endocrinol Metab 2003;88:1516–22.
65. Samsioe G, Bryman I, Ivarsson E. Some anthropological aspects of the climacteric syndrome. Acta Obstet Gynecol Scand Suppl 1985;130:5–7.
66. Haines CJ, Chung TK, Leung DH. A prospective study of the frequency of acute menopausal symptoms in Hong Kong Chinese women. Maturitas 1994;18:175–81.
67. Tang GW. The climacteric of Chinese factory workers. Maturitas 1994;19:177–82.
68. Lock M. Contested meanings of the menopause. Lancet 1991;337:1270–2.
69. Lock M, Kaufert P, Gilbert P. Cultural construction of the menopausal syndrome: the Japanese case. Maturitas 1988;10:317–32.
70. Gold EB, Sternfeld B, Kelsey JL, Brown C, Mouton C, Reame N, et al. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40-55 years of age. Am J Epidemiol 2000;152:463–73.
71. Freeman EW, Sammel MD, Gracia CR, Kapoor S, Lin H, Liu L, et al. Follicular phase hormone levels and menstrual bleeding status in the approach to menopause. Fertil Steril 2005;83:383–92.
72. Manson JM, Sammel MD, Freeman EW, Grisso JA. Racial differences in sex hormone levels in women approaching the transition to menopause. Fertil Steril 2001;75:297–304.
73. Gracia CR, Freeman EW, Sammel MD, Lin H, Nelson DB. The relationship between obesity and race on inhibin B during the menopause transition. Menopause 2005;12:559–66.
74. Seifer DB, Maclaughlin DT. Mullerian inhibiting substance is an ovarian growth factor of emerging clinical significance. Fertil Steril 2007;88:539–46.
75. Seifer DB, Maclaughlin DT, Christian BP, Feng B, Shelden RM. Early follicular serum mullerian-inhibiting substance levels are associated with ovarian response during assisted reproductive technology cycles. Fertility and Sterility 2002;77:468–71.
76. van Rooij IA, Tonkelaar I, Broekmans FJ, Looman CW, Scheffer GJ, de Jong FH, et al. Anti-mullerian hormone is a promising predictor for the occurrence of the menopausal transition. Menopause 2004;11:601–6.
77. Tremellen KP, Kolo M, Gilmore A, Lekamge DN. Anti-mullerian hormone as a marker of ovarian reserve. Aust N Z J Obstet Gynaecol 2005;45:20–4.
78. de Vet A, Laven JS, de Jong FH, Themmen AP, Fauser BC. Antimullerian hormone serum levels: a putative marker for ovarian aging. Fertil Steril 2002;77:357–62.
79. Butts S, Seifer DB. 6 office tests of ovarian reserve and what they can tell you. OBG Management 2008;20:29–40.
80. Hehenkamp WJ, Looman CW, Themmen AP, de Jong FH, Te Velde ER, Broekmans FJ. Anti-Mullerian hormone levels in the spontaneous menstrual cycle do not show substantial fluctuation. J Clin Endocrinol Metab 2006;91:4057–63.
81. La Marca A, Stabile G, Artenisio AC, Volpe A. Serum anti-Mullerian hormone throughout the human menstrual cycle. Hum Reprod 2006;21:3103–7.
82. La Marca A, Giulini S, Orvieto R, De Leo V, Volpe A. Anti-Mullerian hormone concentrations in maternal serum during pregnancy. Hum Reprod 2005;20:1569–72.
83. Tsepelidis S, Devreker F, Demeestere I, Flahaut A, Gervy C, Englert Y. Stable serum levels of anti-Mullerian hormone during the menstrual cycle: a prospective study in normo-ovulatory women. Hum Reprod 2007;22:1837–40.
84. Somunkiran A, Yavuz T, Yucel O, Ozdemir I. Anti-Mullerian hormone levels during hormonal contraception in women with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2007;134:196–201.
85. Seifer DB, Golub ET, Lambert-Messerlian G, Benning L, Anastos K, et al. Variations in serum mullerian inhibiting substance between white, black, and Hispanic women. Fertil Steril 2009;92:1674–8.
86. Freeman EW, Gracia CR, Sammel MD, Lin H, Lim LC, Strauss JF 3rd. Association of anti-mullerian hormone levels with obesity in late reproductive-age women. Fertil Steril 2007;87:101–6.
87. Grisso JA, Freeman EW, Maurin E, Garcia-Espana B, Berlin JA. Racial differences in menopause information and the experience of hot flashes. J Gen Intern Med 1999;14:98–103.
88. Freeman EW, Sammel MD, Lin H, Gracia CR, Pien GW, Nelson DB, et al. Symptoms associated with menopausal transition and reproductive hormones in midlife women. Obstet Gynecol 2007;110:230–40.
89. Freeman EW, Grisso JA, Berlin J, Sammel M, Garcia-Espana B, Hollander L. Symptom reports from a cohort of African American and white women in the late reproductive years. Menopause 2001;8:33–42.
90. Gold EB, Colvin A, Avis N, Bromberger J, Greendale GA, Powell L, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. Am J Public Health 2006;96:1226–35.
91. Goldsmith LT, Kim S, Lasser NL, McGovern P, Weiss G. Menopausal symptom relief in women's health initiative participants given estrogen: reduced efficacy of estrogen in black women. Reprod Sci 2009;16.
92. Kaplowitz PB, Slora EJ, Wasserman RC, Pedlow SE, Herman-Giddens ME. Earlier onset of puberty in girls: relation to increased body mass index and race. Pediatrics 2001;108:347–53.
93. Adair LS, Gordon-Larsen P. Maturational timing and overweight prevalence in US adolescent girls. Am J Public Health 2001;91:642–4.
94. Wang Y. Is obesity associated with early sexual maturation? A comparison of the association in American boys versus girls. Pediatrics 2002;110:903–10.
95. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. JAMA 2004;291:2847–50.
96. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. JAMA 2006;295:1549–55.
97. Census of Population Public Law 94–171 Redistricting Data File: Race, US Census Bureau.
98. Grieco EM, Cassid RC. Overview of Race and Hispanic Origin: Census 200 Brief, US Census Bureau.
99. Stephen EH, Chandra A. Declining estimates of infertility in the United States: 1982–2002. Fertil Steril 2006;86:516–23.
100. Maheshwari A, Stofberg L, Bhattacharya S. Effect of overweight and obesity on assisted reproductive technology—a systematic review. Hum Reprod Update 2007;13:433–44.
101. Wang JX, Davies MJ, Norman RJ. Obesity increases the risk of spontaneous abortion during infertility treatment. Obes Res 2002;10:551–4.
102. Fedorcsak P, Storeng R, Dale PO, Tanbo T, Abyholm T. Obesity is a risk factor for early pregnancy loss after IVF or ICSI. Acta Obstet Gynecol Scand 2000;79:43–8.