EDITORIAL COMMENT

(Age is the single best predictor of outcome after treatment for infertility, irrespective of diagnosis. Ovarian reserve and oocyte developmental potential both decline with advancing age, contributing to the misconception among doctors and patients alike that reproductive aging is mediated by decreasing ovarian reserve. Mounting evidence, however, suggests that ovarian reserve and oocyte quality are related to each other only loosely, if at all. The study by Hvidman et al adds to this literature by investigating whether measures of ovarian reserve differ between infertile patients and age-matched normal controls with no history of infertility. Subjects with polycystic ovary syndrome were excluded. Transvaginal ultrasonography on CD 2–5 estimated mean ovarian volume and AFC. After adjusting for age, AMH levels or AFC did not differ between the 2 cohorts. Therefore, fertile women below the age of 40 years have the same age-related depletion of ovarian reserve as infertile women of the same ages.—DK)

Anti-Müllerian Hormone Serum Concentrations of Women With Germline BRCA1 or BRCA2 Mutations

Kelly-Anne Phillips, Ian M. Collins, Roger L. Milne, Sue Anne McLachlan, Michael Friedlander, Martha Hickey, Catharyn Stern, John L. Hopper, Richard Fisher, Gordon Kannemeyer, Sandra Picken, Charmaine D. Smith, Thomas W. Kelsey, and Richard A. Anderson, for the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab)

Division of Cancer Medicine, Peter MacCallum Cancer Centre, East Melbourne (K.-A.P., I.M.C., S.A.M., R.F., S.P., C.D.S.); Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville (K.-A.P.); Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, School of Population Health, The University of Melbourne, Parkville (K.-A.P., R.L.M., J.I.H.); Department of Medicine, St Vincent’s Hospital, The University of Melbourne, Parkville (K.-A.P., S.A.M.); School of Medicine, Faculty of Health, Deakin University, Geelong (I.M.C.); Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne (R.L.M.); Department of Medical Oncology, St Vincent's Hospital, Fitzroy (S.A.M.); Prince of Wales Clinical School, University of New South Wales, Sydney (M.F.); Department of Medical Oncology, Prince of Wales Hospital, Randwick (M.F.); Department of Obstetrics and Gynecology, the Royal Women's Hospital, Parkville (M.H., C.S.); Melbourne IVF, East Melbourne (G.K., G.K.); Australia; School of Computer Science, University of St Andrews, Fife (T.W.K.); and Medical Research Council Centre for Reproductive Health, Queen’s Medical Research Institute, University of Edinburgh, Edinburgh (R.A.A.), United Kingdom

Hum Reprod 2016;31:1126–1132

ABSTRACT

Increased risks of female breast cancer, ovarian cancer, fallopian tube cancer, and primary peritoneal cancer have been attributed to germline mutations in the BRCA1 or BRCA2 genes. These also have an impact on ovarian reserve and fertility in women. The best available biomarker to forecast reproductive lifespan and related conditions is levels of circulating anti-müllerian hormone (AMH). This study, conducted in 1997, was done to assess whether women with a mutation in BRCA1 or BRCA2 have reduced ovarian reserve as compared with women who do not carry a BRCA1 or BRCA2 mutation, by measuring circulating AMH concentrations. Six hundred ninety-three participants in the age group of 25 to 45 years were chosen from those women recruited to the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab) Cohort Study and who either had a pathogenic mutation, splice site mutation, or large deletion in BRCA1 or BRCA2 (mutation carriers), or were a blood relative of a mutation carrier and had themselves been tested and found not to carry the identified family-specific mutation (noncarriers). Plasma samples collected and stored were analyzed at the Melbourne IVF Endocrine Laboratory, and AMH concentrations were measured between November 2014 and January 2015.
The study found that BRCA1 mutation carriers had 25% (95% confidence interval, 5%–41%, P = 0.02) lower AMH concentrations than noncarriers and that the AMH concentrations were most seen in the lowest quartile for age (odds ratio, 1.84; 95% confidence interval, 1.11–3.03; P = 0.02). No association between AMH concentration and BRCA2 mutation status (P = 0.94) was found. The study concluded that women with a germline mutation in BRCA1 may have reduced ovarian reserve, with potential implications for fertility and reproductive lifespan.

EDITORIAL COMMENT

(The BRCA1 or BRCA2 genes encode proteins involved in DNA double strand break repair and germline mutations in these genes increase the risk of a number of cancers. Impaired DNA double strand break repair, from germline mutations in these genes, would be expected also to disrupt female reproductive function because oocytes are long-lived, postmitotic cells that do not regenerate after the fetal stage of oogenesis. Results of studies on the effects of BRCA1 and BRCA2 mutations on ovarian reserve and fertility have been conflicting. Fertility is a particularly challenging phenotype to study because most modern women have ready access to contraception, and the identification of a cancer causing mutation must influence the decision about whether to build a family. Study of the effect of BRCA mutations on ovarian reserve also is challenging because of the difficulty identifying adequate controls. Blood relatives make excellent controls because reproductive aging is a highly heritable trait. However, BRCA mutation status of blood relatives is not always known. The study by Phillips et al used blood relatives with known BRCA status, identified from a registry, as controls. Subjects with a mutation in BRCA1 or BRCA2 were identified from a familial breast cancer (kConFab) registry. Controls were blood relatives who tested negative for mutations in these genes. The authors estimated ovarian reserve by measuring AMH, the most reliable estimate available for ovarian reserve. BRCA1 mutation carriers had 25% lower AMH concentrations than noncarriers. Moreover, AMH concentrations in BRCA mutation carriers clustered in the lowest quartile for age. BRCA2 mutation status did not affect AMH level. This study demonstrates reduced ovarian reserve in women with germline BRCA1 mutations. This large, well-designed study provides valuable information to council women with BRCA mutations about their fertility and reproductive lifespan.—DK)