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# BRCA1 gene mutation is linked to women having fewer eggs in their ovaries

April 19 2016

Researchers have discovered a link between the BRCA1 gene mutation and lower levels of a hormone that is an indicator of the number of eggs left in a woman's ovaries, according to research published today (Wednesday) in *Human Reproduction*, one of the world's leading reproductive medicine journals.

In the first large study looking at BRCA1 and BRCA2 genetic mutations and levels of anti-Müllerian hormone (AMH) in women who carry the mutated genes, the group of international researchers found that carrying the BRCA1 mutation was associated with AMH concentrations that were, on average, 25% lower than those in non-carriers. The effect was not seen in women with the BRCA2 mutation.

Professor Kelly-Anne Phillips, a consultant medical oncologist at the Peter MacCallum Cancer Centre in East Melbourne (Victoria, Australia) and the first author of the study, said: "This means that women in their mid-30s, who carry the BRCA1 mutation, have, on average, ovarian reserves similar to those of non-carriers who are two years older."

Although AMH is a reliable marker of ovarian reserve, Prof Phillips said: "It's important to remember that AMH is only one indicator of a woman's potential fertility, the ability to conceive and carry a baby to full term is affected by many other factors as well, including egg quality and whether the fallopian tubes are unobstructed, neither of which are measured by AMH. Women with low AMH levels can sometimes still have a baby and, conversely, women with high AMH levels are

sometimes unable to do so.

"However, our findings suggest that women carrying the BRCA1 mutation should try to avoid delaying pregnancy until their late 30s or 40s when fertility is reduced anyway because of their age. For women trying to conceive in their 20s, any difference in ovarian reserve between BRCA1 mutation carriers and non-carriers is unlikely to be of clinical significance."

Women who carry the BRCA1 and BRCA2 gene mutations have a higher risk of cancers in the breast, ovaries, fallopian tubes and peritoneum. The risk increases with age and is generally higher for those with the BRCA1 mutation than with the BRCA2 mutation. The mutations are rare in the general population - about 0.1% for BRCA1 and 0.2% for BRCA2 - although they can be more prevalent in certain groups, such as Ashkenazi Jews. As mutation carriers enter their early 40s they are usually advised to have their ovaries and fallopian tubes removed in order to minimise their cancer risk (as these cancers are hard to detect in their early stages when they are easier to treat). For this reason, many women who know they are carriers try to have their children when they are younger. However, until now, there has been little good-quality evidence about the effects of these genetic mutations on non-cancer-related conditions such as fertility.

Prof Phillips and colleagues from research centres in Australia and Scotland (UK), analysed AMH levels from 693 women, aged between 25-45 years (average age was 35), who had no personal history of cancer but who had enrolled into the Australian and New Zealand Kathleen Cuningham Foundation Consortium for research into Familial Breast Cancer (kConFab) study between 1997 and 2012. A total of 172 women were carriers and 216 women non-carriers from families carrying the BRCA1 mutations, and 147 carriers and 158 non-carriers were from families with the BRCA2 mutations. The women retained both ovaries

and were not pregnant or breast-feeding at the time that blood was taken from them. The researchers adjusted their results to take account of age, oral contraceptive use, body mass index and smoking.

In addition to BRCA1 mutations carriers having 25% lower AMH concentrations, on average, than non-carriers, they were also more likely to have AMH concentrations that placed them in the lowest quarter when the women were divided into four groups according to the AMH levels. This was not seen in BRCA2 mutation carriers.

In their *Human Reproduction* paper, the authors say that a possible mechanism for the link between the BRCA1 mutation and ovarian reserve may be the role played by both the mutations in DNA repair - inefficient DNA repair has been shown to contribute to the aging of a woman's eggs. BRCA1 and BRCA2 are both integral to mending breaks that occur in both strands of the DNA helix.

"BRCA2 has a more limited role in double-strand DNA break repair compared with BRCA1 and BRCA2 mutation carriers tend to develop fewer cancers and at a later age, compared with BRCA1 mutation carriers," explained Prof Phillips. "So it is credible that any effect of mutation status on ovarian reserve would be more pronounced in BRCA1 mutation carriers. There may be a lesser effect in BRCA2 mutation carriers as well, but our study did not have adequate power to detect it."

The researchers say that their findings also raise the hypothesis that BRCA1 mutations carriers may have a higher than average risk of chemotherapy-induced menopause. "The hypothesis is that if BRCA1 mutation carriers have lower ovarian reserve than their non-carrier counterparts when they start chemotherapy for cancer treatment, the carriers may be more likely to develop menopause associated with the chemotherapy. However, this is just a hypothesis at this stage and

requires further research," she concluded.

**More information:** "Anti-Müllerian hormone serum concentrations of women with germline BRCA1 or BRCA2 mutations", by Kelly-Anne Phillips et al. *Human Reproduction*. DOI: 10.1093/humrep/dew044

Provided by European Society of Human Reproduction and Embryology