Journal of
Gynecology and Women's Health
ISSN 2474-7602

Juniper Publishers
key to the Researchers

Opinion
Volume 4 Issue 4 - May 2017
DOI: 10.19080/JGWH.2017.04.555646

J Gynecol Women's Health

Let's Slow Down the Race for Oocyte Donation: A Plea for Better Management of Young Women with Reduced Ovarian Reserve

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Submission: May 09, 2017 ; **Published:** May 23, 2017

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Opinion

Oocyte donation is an important option for menopausal women who wish to bear a child, and is particularly important for those suffering premature menopause. Concerns have recently been raised regarding the increased risk of cancer in young oocyte donors, and this growing part of assisted reproduction now merits considered scientific review, leaving aside any reference to ethical aspects that may surround the procedure.

Two areas of current concern include:

The yield of babies born per oocyte retrieved

An excellent study by Martin et al. [1] demonstrated that, at best, only 15% of oocytes retrieved lead to a live birth, even in specially selected populations of oocyte donors. Several different factors probably contribute to this disappointingly poor outcome and its associated oocyte wastage: controlled ovarian stimulation has been shown to induce epigenetic/methylation defects in the oocyte [2,3], and since *in vitro* conditions are far from optimal with respect to maintenance of methylation/epigenetic marks, manipulation of gametes during culture probably also has a further negative impact [4-7]. Careful and considered revision of protocols for controlled ovarian stimulation is long overdue, especially since the quest to retrieve large numbers of oocytes may put young donors at risk of developing symptoms of ovarian hyperstimulation.

Risks for the oocyte donors

According to Schneider et al. [8], "a positive association exists between [endogenous] sex hormones and breast cancer risk in premenopausal women." The risk could potentially be even more relevant for endometrial pathologies. Clearly, long-term reliable follow-up studies of young egg donors are not available, but questions regarding potential risks do need to be raised. Estrogens are well known inducers of oxidative stress (OS), and a clear link has been established between both oxidative stress and methylation errors, as well as between methylation anomalies and cancer [9].

The endemic presence of endocrine disruptors (EDCs) in the ambient environment is a further area of increasing concern. These compounds are present in the urine of large populations of female patients who are trying to conceive [10]. Plastic-derived endocrine disruptors include bisphenol A (BPA) di-ethyl and di-butyl phtalates (DEHP & DBP), and these compounds generate OS that can induce epigenetic changes via anomalous DNA methylation [11-13]. The EDC status of egg donors should be evaluated as part of routine baseline/screening assessments.

In addition, patients who carry isoforms of methylene tetrahydrofolate-reductase (MTHFR) have a decreased methylation capacity due to impaired folic acid metabolism, which is mandatory for the process of methylation and for DNA stability and repair. Oocyte donors are not necessarily routinely tested for MTHFR polymorphisms - this varies from country to country. Oocyte recipients and their male partners should also be tested for MTHFR isoforms. The MTHFR C677T isoform can induce anomalies in sperm nucleus condensation, which can lead to miscarriages. MTHFR polymorphisms also have an impact on embryo quality [14].

Encouraging strategies are now available that may help to decrease the requirement for donated oocytes, via reducing the incidence of anomalies in epigenetics/methylation in the

infertile patients that may be linked to EDCs. Animal experiments have clearly shown that nutritional support of the one-carbon cycle by administering B-group vitamins and Zinc can reverse the negative impact of EDCs [15]. This has been shown to increase the spontaneous pregnancy rate in patients with repeated implantation failure after ART [9,16,17], and has also been reported to support DNA repair mechanisms in patients with breast cancer who are being treated with Tamoxiphen [18]. Similarly, animal experiments have demonstrated that some compounds which are known to prevent oxidative stress may to some extent reverse the effects of premature oocyte ageing [19]. The one-carbon cycle is involved in the synthesis of major protective molecules such as CoQ10, glutathione and hypotaurine, and the cycle plays a key role in preventing the detrimental processes that contribute to reproductive ageing, and oocyte ageing in particular.

Oocyte donation has become increasingly popular worldwide as first-line treatment for women with reduced ovarian reserve, and in many countries is practiced with commercial gain for both the ART clinics who offer it, and for the young oocyte donors. However, although data regarding controlled ovarian stimulation for IVF globally may be reassuring, potential long-term risks for the donors should not be ignored, especially in the case of young women for whom this intervention does not represent a 'treatment' required for their own medical benefit; other options should first be explored in order to improve ovarian function in women with a reduced ovarian reserve.

Assessment of methylation/imprinting processes in both female and male partners should be considered, and in particular the negative impact of MTHFR polymorphisms. Nutritional supplementation with 5 Methyl THF, the metabolite downstream of MTHFR, is a useful strategy for these patients. Investigation of urinary EDC levels should not be overlooked, inorder to understand and possibly overcome or bypass potential gamete pathologies.

In conclusion, we suggest that oocyte donation is not the inevitable path for patients with diminished ovarian reserve associated with low serum AMH, even for those in their late thirties; consideration of other options is in the best interest of both the donors and their recipients.

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How to cite this article: Cornet D, Alvarez S, Jacquesson-Fournols L, Cohen M, Elder K, et al. Let's Slow Down the Race for Oocyte Donation: A Plea for Better Management of Young Women with Reduced Ovarian Reserve. J Gynecol Women's Health. 2017; 4(4): 555646. DOI: 10.19080/JGWH.2017.04.555646.

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