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Editorial

Breast cancer risk after oocyte donation: should we really be concerned?

The rapidly increasing utilization of oocyte donation in developed countries seems directly related to a delay in the age of childbirth by an ever increasing proportion of women. In their 15th European IVF-monitoring survey, the European Society of Human Reproduction and Embryology (ESHRE) reported 17,728 fresh oocyte donation cycles in 2012 (ESHRE et al, 2016), an increase of over 10% compared with 2010. Similar trends can be observed in the United States, where the annual number of oocyte donation cycles increased from 10,801 to 19,988 between the years 2000 and 2010 (Kawwass et al, 2013). At present, oocyte donation cycles represent over 10% of all IVF cycles performed in the United States (Practice Committee of the American Society for Reproductive Medicine, Practice Committee of the Society for Assisted Reproductive Technology, 2014).

The rapidly growing demand for oocyte donors raises questions regarding appropriate counselling, risk disclosure and informed consent in relation to potential physical, emotional, legal and social risks, along with possible long-term health implications (Alberta et al., 2014; Klitzman, 2016). To ensure quality of care and appropriate protection of the interests of oocyte donors, both the American Society for Reproductive Medicine (ASRM) and ESHRE have published a number of guidelines concerning oocyte donation programs that address important issues such as genetic screening and the need to develop 'prudent' approaches to minimize risks, alongside stressing the obligations and rights of oocyte donors (ESHRE Task Force on Ethics and Law et al, 2007; Ethics Committee of the American Society for Reproductive Medicine, 2009; Dondorp et al., 2014; Practice Committee of the American Society for Reproductive Medicine, Practice Committee of the Society for Assisted Reproductive Technology, 2014). However, it has been reported that these guidelines are not followed by approximately 50% of centers in the United States when recruiting oocyte donors online (Keehn et al., 2012).

In the current issue of *RBM Online*, Schneider and colleagues (Schneider et al., 2017) report five case histories of women diagnosed with breast cancer at a young age several years after undergoing ovarian stimulation as oocyte donors. The authors suggest a direct causal relationship between ovarian stimulation and the subsequent development of breast cancer, question the current practice of oocyte donation and argue in favour of a separate oocyte donor registry to assess long-term health risks. Indeed, only limited (though reassuring) evidence is available concerning the long-term health of oocyte donors undergoing ovarian stimulation (Soderstrom-Anttila et al., 2016). Conversely, multiple large sample-size studies involving tens of thousands of women, with extended follow-up periods of up to 30 years exist that establish convincingly the long-term safety of IVF treatment (Sergentanis et al., 2014, Practice Committee of the American Society for Reproductive Medicine. Electronic address and Practice Committee of the American Society for Reproductive Medicine, 2016; van den Belt-Dusebout et al., 2016). Moreover, no association between breast cancer risk and age at the time of IVF could be established in a recent long-term follow-up of more than 25,000 women (van den Belt-Dusebout et al., 2016).

Although the occurrence of breast cancer in five women following oocyte donation as reported by Schneider appears worrying, the possibility of inclusion bias cannot be ignored since the authors state that they were approached by the women over a period of several years. A closer look at their specific case reports reveals that the age of the women ranged between 21 and 34 years, a large number of oocytes were often retrieved (28–33 oocytes) and the women underwent up to 10(!) ovarian stimulation cycles. Ovarian hyperstimulation syndrome (OHSS) occured on multiple occasions, and twice in one woman. In addition, one woman actually started IVF for infertility treatment and converted to oocyte donation for personal reasons later on. These case reports demonstrate that guidelines concerning oocyte donation are not always followed, and that the approaches used in these case cannot be considered as 'prudent'. Indeed, concerns of exploitation related to gamete donation have been expressed earlier (Ethics Committee of the American Society for Reproductive Medicine, 2009). Stimulation of a large quantity of growing follicles (coinciding with extremely high oestrogen production), undergoing up to 10 stimulation cycles, and the development of OHSS may all independantly represent risk factors for developing breast cancer, rather than oocyte donation procedures *per se*, although this is merely a speculation not supported by evidence from the literature.

Overall, the life-time risk for breast cancer in women is 12% (www.breastcancer.org), and approximately 10% of women diagnosed with breast cancer are younger than 40 years old (DeSantis et al., 2016). Knowing that 1% of women in the general population will be diagnosed with breast cancer before the age of 40, along with the assumption that 20,000 oocyte donation cycles – as performed annually in the United States – may represent at least 5000 women undergoing

http://dx.doi.org/10.1016/j.rbmo.2017.03.005

ovarian stimulation for oocyte donation, as many as 50 of these women may subsequently be diagnosed with breast cancer at a young age due to the population risk alone. So yes, there will be oocyte donors (and IVF patients) who unfortunately develop breast cancer in their lives but most likely, and according to the most recent published evidence, their chance of doing so will be similar to that of women in the general population who did not undergo ovarian stimulation.

Reassuring long-term safety data obtained from women undergoing IVF for infertility treatment may not necessarily be valid for oocyte donors. Socio-demographics, motivation and fertilty characteristics of oocyte donors have, to some extent, been studied (Bracewell-Milnes et al., 2016; Greenfeld, 2008; Pennings et al., 2014). Oocyte donors may differ from infertile women undergoing IVF. Oocyte donors are usually younger and fertile. Infertility *per se* may affect cancer risk. However, a large proportion of IVF cycles are performed exclusively for male-factor infertility, diminished ovarian reserve, preimplantation genetic diagnosis, and other reasons not directly related to female infertility. Those women are not only fertile, but are usually younger than women with female infertility and, thus, may more closely resemble the profile of oocyte donors.

Breast cancer risk is increased in women with early menarche and late menopause, a personal or a family history of breast cancer, gene alterations such as *BRCA1* or *BRCA2* mutations, a history of radiation exposure before the age of 30 and in women with regular consumption of alcohol. In contrast, a full-term pregnancy before the age of 30 and regular exercise reduces breast cancer risk (www.breastcancer.org). Most of these risk factors for breast cancer, of course, preclude women from being selected as egg donors.

In the absence of appropriate data, it is not possible to state with absolute certainty that volunteering as an oocyte donor will not increase breast cancer or other health risks. Indeed, the 'absence of proof' is not the same as 'the proof of absence'. Safety should always be of major concern in relation to any medical intervention, but especially in the case of volunteers undergoing potentially hazardous procedures solely to help others. On the other hand, even young healthy women may be confronted with serious health hazards irrespective of whether they undergo medical treatment or not. Such concerns are the major reason for our decision to publish the extended case history presented by Schneider and colleagues which, no doubt, will attract much attention. We welcome further discussion on this topic and feel that both short- and long-term safety of any infertility intervention should be given a high priority. However, it can be stated with some degree of confidence that the data currently available and the overall risk calculations do not support the notion of increased breast cancer risk in oocyte donors. This is a call to scientific societies and regulatory bodies: Good registry data of oocyte donor follow-up are indeed required to generate robust information which will hopefully put this issue to rest.

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