Fertility preservation in women: exploring clinical dilemmas
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CHAPTER 8

General discussion
The Greek myth of Daedalus and Icarus tells the story of a father and son who are imprisoned on the isle of Crete. Daedalus, a resourceful genius, invents a tool that would enable release from captivity: two wings of feathers, held together with wax by which his son, Icarus, is instructed to fly. “Don’t fly too low, or too high,” he tells his son “keep a middle range, and do not show off”. With these remarks Icarus, initially, flies with caution. But soon, he wonders what he can do with this splendid toy, what limits there are to his father’s invention. It is exciting, wonderful fun, but he does not notice the wax of his wings is melting and feathers are falling out.” Tragically, Icarus dies after falling into the sea (Jones 2007).

In analogy with this myth, excitement about being able to cryopreserve oocytes after a long time of research and development warrants thoughtfulness on its clinical application.

According to the principles of evidence-based medicine, proper clinical care requires information on safety and effectiveness acquired after careful evaluation research. However, evaluation research is largely lacking as illustrated by chapter four, in which we found no randomized controlled trials after a systemic literature search on the topic of safety and efficacy of controlled ovarian stimulation in women with breast cancer. The reason that evaluation research is lacking in this field could be related to idiosyncratic nature of fertility preservation: there is a - potentially large - time-gap between the moment of cryopreservation and the moment of thawing. Fertility preservation is therefore only the first half of a procedure, of which the second half - thawing - does not necessarily have to take place. How to define the study population, the interventions and the outcome measures in research in the field of fertility preservation therefore deserves further thought.

**Defining the study population**

Identifying the study population for fertility preservation is challenging as all women are subject to the physiological characteristic of age-related decline of fertility and therefore can benefit from fertility preservation (Faddy et al., 1992). Current clinical practice uses the subdivision between medical and non-medical indications for fertility preservation. We have shown in chapter six that women with breast cancer dreaded having to delay pregnancy for two to five years due their breast cancer treatment, as they were aware of their age-related risk for sub- or infertility. Aborting the term ‘social’ or ‘non-medical’ indications in discussions on nomenclature for oocyte cryopreservation would acknowledge the overlap of medical and non-medical indica-
tions (Stoop et al., 2014; Martin 2011). This classic distinction between women who have a medical risk factor for premature ovarian insufficiency (POI) or who have a ‘non-medical’ risk factor for infertility is questionable. Premature ovarian insufficiency is a rigid term that is based on a biological perception of ovarian ‘failure’ that occurs before the age of 40 years. This concept disregards women’s social and relational context in which women are not always in the right circumstances to conceive before the age of 40 (i.e. due to lack of male partner), making them at risk for ovarian insufficiency by the time they are able to conceive. These women may well feel at risk for ‘premature’ ovarian insufficiency, as premature in this context means ‘before being in the right circumstances to conceive’.

Another issue to consider is how to identify patients potentially benefitting from a risk-reducing therapy, since fertility preservation does not treat a disease, but targets the eventuality of a disease, namely infertility. In that sense, fertility preservation can be sided with other ‘risk-reductive’ or ‘preventive’ medical therapies such as cholesterol reducing drugs for persons at risk of heart disease or prophylactic antibiotics in persons at risk of infection. For women seeking fertility preservation, there are presently no evidence- or consensus based cut-off levels at hand. Quantifying the risk on premature ovarian insufficiency for which fertility preservation is performed is thus necessary. Standardized ovarian reserve testing prior to fertility preservation and at several moments within the time-gap inherent to fertility preservation may be of help. This longitudinal follow up of ovarian reserve testing is the first step towards predicting who will or will not benefit from fertility preservation. Recently, Anti-Müllerian Hormone (AMH) has been proved to be a marker for ovarian reserve (Broer et al., 2014). AMH has also been mentioned to be a marker for the level of gonadotoxicity in young women with cancer (Fabbri et al., 2014; Broughman et al., 2012). Furthermore, pre-treatment AMH has been demonstrated to correlate with post chemotherapy AMH level (Dillon et al., 2013). The paradigm of assessing ovarian reserve prior to a time-gap in which women are not reproducing has also been mentioned in women starting oral contraception (Kushnir et al., 2014). Collecting this information can help setting up evaluation research in terms of effectiveness of treatment and classify risk-categories.

Whether the benefits of fertility preservation in terms of effectiveness outbalance the costs, remains unknown. Prediction models have been proposed, that use decision analysis to estimate cost effectiveness of oocyte cryopreservation for ‘non-medical’ reasons. However cohort studies with the aim to assess cost-effectiveness are not yet performed, because only few women have returned to use their banked oocytes - as
also indicated by chapter 7 (Hirschfeld-Cytron et al., 2012; Loendersloot et al., 2011). More research is thus needed to evaluate the cost-effectiveness of oocyte banking for so called ‘non-medical reasons’.

With the loud call that fertility preservation should be integrated into the regular treatment trajectory for cancer (Wallace, 2011; Waimey et al., 2013; Kong et al., 2011), this integration may imply that in the future fertility preservation will not only take place prior to cancer treatment but also after cancer treatment. As cancer therapy is often multifaceted, one might argue that women who have high chances on relapse of disease can benefit from multiple fertility preservation-trajectories even when these are interrupted by chemotherapy. Future cancer guidelines should take this into account when mentioning timing of performing fertility preservation.

Defining the intervention

Fertility preservation consists of several techniques that have a common goal but differ completely in their execution and consequences. For example, cryopreservation of ovarian tissue after minimal invasive surgery aims to ‘store’ a large part of ovarian reserve that would otherwise serve a physiological role, whereas by cryopreservation of oocytes one aims to ‘store’ a fraction of ovarian reserve that would be lost in time anyway. After reimplantation of thawed ovarian tissue, conception can theoretically be instigated by the in situ (non-transplanted) ovary. Thorough monitoring of the ovaries is thus required when effectiveness of this procedure is to be evaluated.

Clinics differ in their policy of who should be offered cryopreservation of ovarian tissue; some clinics reserve this option for women with a predefined high risk of chemotherapy-induced menopause, while others offer the procedure to any woman opting for it, even in absence of malignant disease. Some clinics offer a combination of several fertility preserving techniques, resulting in a future in which women will have a combination of various reproductive materials stored i.e. cryopreserved ovarian tissue and oocytes (mature or immature) or embryos. Hence, tracing back the origin of conception in case of an achieved pregnancy after thawing and using multiple techniques will be a difficult task when thorough monitoring is lacking. Registering patients undergoing fertility preservation and performing long-term follow up is therefore necessary. The initiative of ESHRE to set up international registries for fertility preservation is encouraging and can provide essential information for evaluation research. To tackle the problem of confounding in evaluation research in fertility preservation, the registry should incorporate frequent moments of follow-up
similar to how the national cancer registry in the Netherlands operates. Considering the issue on safety of fertility preservation in women with breast cancer, connecting these two registries on a patient-level could provide relevant information. The long-term follow up of the STIM-trial presented in chapter 5 intends to use this approach. Although this seems a simple solution, a great change in mind-set is required to reach this goal which entails the concept of fertility preservation not ending with cryopreservation but starting with cryopreservation, as is also expressed by other authors (Quinn and Vadaparampil, 2013).

**Defining the outcome measures**

Women who underwent fertility preservation differ from subfertile patients as they carry an unknown risk to become subfertile after fertility preservation, but after fertility preservation can appear to be fully capable of conceiving naturally, as has been shown in chapter 7. It has recently been proposed that the dichotomization between fertility and subfertility is flawed as -despite lack of conception within one year- many ‘subfertile’ couples are able to conceive naturally but only take longer to do so (McLernon *et al.*, 2014). Subfertility therefore represents a prognosis rather than an absolute diagnosis, and this prognosis should also be taken into account when designing research assessing the effect of fertility preservation.

In chapter seven we found that out of the 68 women that banked their oocytes for medical reasons, 16 were trying to conceive naturally and 48 women (71%) reported to have intentions of using cryopreserved oocytes only if natural conception failed. Several studies indicated that chances of natural conception are often retained after chemotherapy (Barton *et al.*, 2013; Nielsen *et al.*, 2013; Schmidt *et al.*, 2013). With regard to retaining (part) of the natural reproductive potential after fertility preservation, one must think about how to value the issue of leftover stored oocytes when women complete family planning after natural conception or decide not to have children at all. Are leftover stored oocytes in this case a negative outcome, because women underwent a costly and risky treatment that in itself did not lead to pregnancy? Or is this a positive outcome if fertility preservation is considered an insurance against future sterility, thereby legitimating obtaining a surplus of oocytes? Apart from autologous use, leftover stored oocytes from women with cancer can serve limited other purposes as scrutiny is warranted when oocytes of women with -potentially hereditary- cancer are to be used for heterologous donation. This implies that leftover stored oocytes can only be used for laboratory science or will be wasted.
far, the issue of leftover stored oocytes is paid little attention as fertility preservation is often performed without considering long-term implications. Qualitative research can provide relevant insight in how women approach these questions. This insight can lead to a more general concept of the meaning of surplus gametes for women and may reveal what plans women have for these surplus gametes. This way clinicians can be better prepared for future clinical dilemma’s.

**Clinical implications**

With this in mind, we must take our responsibility when counseling patients in an era vacant of evidence-based information about fertility preservation. When we fully acknowledge that we are currently only offering fertility preservation to women because no one knows what reproductive future lies ahead of them, and when we encourage our patients to participate in evaluation research, we can look forward to a future in which women will be able to make an honest decision that will not leave them disillusioned when the future turns out to be different from what they expected.
References


