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EDITORIAL COMMENTARY

Let's not forget that many prepubertal girls do have other options besides ovarian tissue cryopreservation

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It has become a mantra in articles and conferences on fertility preservation: the only option to preserve the fertility of prepubertal girls undergoing gonadotoxic treatment is ovarian tissue cryopreservation (Jadoul *et al.*, 2010; Revel and Revel-Vilk, 2010; Smitz *et al.*, 2010; Anderson and Wallace, 2011; Fabbri *et al.*, 2012; Rodriguez-Wallberg and Oktay, 2012; Chung *et al.*, 2013; Mintziori *et al.*, 2014). The first healthy live birth after autotransplantation of ovarian tissue harvested during childhood (although not prepubertal) reported in this issue, and thus proof of principle, is likely to reinforce this dogma even further (Demeestere *et al.*, 2015). As a consequence, we can expect a growing number of fertility specialists to be convinced that the offer of cryopreservation of ovarian tissue to young cancer patients should become standard practice.

Fortunately, in the case report of the first live birth, an important nuance was added to the 'only option mantra': 'For prepubertal female patients who face *a high risk of treatment-induced POI*, the only option available to preserve fertility is the cryopreservation of ovarian tissue' [my emphasis]. For those pediatric patients who have a high risk of permanent sterility after their cancer treatment, freezing tissue may indeed be the only way of preserving a chance of future fertility. However, a cautious approach should be adopted for those patients whose treatment regimens imply a substantial risk for premature ovarian failure (POF), but who at the same time have a very small risk of immediate sterility (patients in the medium- or low-risk categories in Wallace *et al.* (2005)). For this group of patients, it is not correct to say that ovarian tissue cryopreservation (OTC) is their only option of preserving their fertility and in fact the idea that OTC is the only option to combat POF is rarely heard in contexts other than that of oncofertility. Another option, besides the advice not to delay parenthood too long, is to bank oocytes once these girls hit puberty if they turn out to be at risk of POF. From an ethical perspective, there are a number of reasons to prefer the option of expectant management combined with oocyte banking over that of OTC.

The advantages of oocyte cryopreservation (OC) after puberty over OTC before puberty follow from the procedures themselves, from the timing and often from an interplay between the two.

First of all, it is ethically problematic to perform an invasive surgical procedure with unknown benefits on minors who cannot give their informed consent. Any surgical intervention carries a risk of surgical complications, infections and the risks associated with anesthesia. Most physicians avoid the latter by removing the ovarian tissue when the patient is anesthetized for a different intervention in the treatment of their disease. However, the other risks remain and are especially worrisome in these patients as their immune systems are already weakened. Also, many young cancer patients have low platelet counts, which is another medical risk factor.

These surgical risks are not the only reason why pediatric oncologists may be reluctant to advise OTC for their young patients. While for some patients cryopreserving ovarian tissue can be perceived as a message of hope, for others, the prospect of yet another surgical intervention can cause additional anxiety in both the child and the parents—who are already overwhelmed by the cancer diagnosis—and thus increase not only the physical, but also the emotional burden.

For the same reason, as previously noted by Wallace *et al.* (2005), it is impossible to respect all the conditions for a valid informed consent at the point in time when it is needed. In the case of minors, one already needs to rely on informed assent and proxy-consent, but even those are difficult to obtain. The intervention often needs to take place shortly after receiving the cancer diagnosis, which, especially in the case of children, is most disturbing and frightening. Patients and their parents have to digest a multitude of information, are focused on survival and are terrified of the prospect of not surviving. They are thus hardly in a good position to weigh all the pros and cons, especially given the very short time frame in which this needs to happen.

Next, let us not forget that the preservation and retransplantation of ovarian tissue from prepubertal girls remains an experimental procedure. Although at least 35 live births have been reported following the transplantation of ovarian tissue from adult patients (Demeestere *et al.*, 2015), uncertainties linger about how the prepubertal tissue will respond when transplanted into an adult woman and about the extent to which the small amounts of tissue available in young girls are a limiting factor for successful treatment. Moreover, the fact that these children have only one ovary left is a concern in itself. If anything happens to the remaining functional ovary (cyst, torsion. . .), the patient ends up with iatrogenic infertility. Another major concern is that autologous transplantation involves a risk of transplanting malignant cells back to the patient.

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In vitro maturation may be a way to avoid this risk, but is not possible at this time.

Finally, especially for the category of patients that we are concerned with here (low to medium risk), there is a considerable chance that ovarian tissue that is frozen at the time of treatment will never be retransplanted. There may be a number of reasons for this. First of all, the patient may still be fertile when she wants to reproduce or her subfertility may be adequately addressed with standard assisted reproductive techniques. As shown in a study by Brougham *et al.* (2012), whereas anti-Mullerian hormone (AMH) levels fell to undetectable concentrations in all girls that were classified as high-risk and did not recover, AMH levels did recover significantly in the medium- and low-risk groups. Another study by Wallace *et al.* (2014) demonstrated that the 'Edinburgh selection criteria' (criteria for who is a good candidate for fertility preservation) are very efficient at selecting those young cancer patients who are truly at risk of losing their fertility (only 8%!) and at identifying those who are not. Moreover, even in the high-risk group, some patients may never desire to embark on parenthood or never find themselves in the right circumstances to do so (which cannot be predicted at a young age), some patients' fertility may be compromised by radiation damage to the uterus or some may not have survived their illness. In all of these cases, we will have submitted a young cancer patient to an invasive procedure without any benefit.

If, instead of freezing ovarian tissue at the time of cancer treatment, we would advise these low to medium-risk girls and their parents to come back to the clinic at age 18 years for an ovarian reserve assessment so that they might still bank oocytes if needed, what would the picture look like then?

With respect to the risks involved, although ovarian stimulation and oocyte retrieval are not risk-free procedures and involve discomfort as well, these interventions are considerably less invasive than the removal of an ovary. The most prominent risk of ovarian stimulation—ovarian hyperstimulation syndrome—has virtually become a risk of the past thanks to the widespread adoption of new stimulation protocols which are especially indicated when all oocytes are frozen (Devroey *et al.*, 2011). The next step of the procedure—oocyte vitrification—is increasingly considered to be an established procedure, although uncertainties about possible long-term effects remain. In any case, it is fair to say that OC is less experimental than OTC, especially when comparing OC for adults with OTC for minors.

Regarding informed consent, the decision to cryopreserve oocytes can now be taken by the patient herself, instead of by her parents. Moreover, it can be taken in a more 'relaxed' atmosphere. The patient's life is not in immediate danger anymore, she has the time to gather and digest all relevant information and time to consider whether or not oocyte cryopreservation is something she desires to pursue.

There are, however, also a number of possible risks associated with relinquishing the chance of cryopreserving ovarian tissue before treatment. In a number of cases, the prediction of the impact of the treatment on the ovarian reserve will be wrong. Some patients, despite starting out in a low- or medium-risk category, will nevertheless end up sterile or only have bad quality oocytes left at age 18 years. Also, an important aspect that remains to be investigated is whether or not a diminished ovarian reserve caused by gonadotoxic treatments should be interpreted in the same way as a diminished ovarian reserve related to aging. If it turns out that these patients have less oocytes, but that the ones they have are of excellent quality (as opposed to reproductively speaking older women), then it may be possible to bank good quality oocytes at puberty. If however, not only the quantity but also the quality of oocytes that these women have left is severely affected, their prospects will be bleaker. Another downside to postponement of the decision to preserve fertility is that once the patient has left the clinic, she may never return. Once a patient has survived cancer, the associated fertility problems may vanish in the background until she attempts to establish a pregnancy, at which point it may be too late to intervene. This may particularly be the case as the original decision to postpone fertility preservation will oftentimes be taken by the parents, rather than by the child herself. Ideally, these young women should get a 'friendly reminder' when they reach puberty. Relying on gynecologists to deliver this message is probably not very effective, as not all adolescents visit gynecologists and many of those who do might fail to inform their gynecologists about the fact that they are childhood cancer survivors. The oncologist is therefore probably better placed, on the condition that the patient still visits the oncologist for regular check-ups.

In conclusion, the first healthy live birth after ovarian tissue freezing in childhood is a great achievement and hopefully this procedure will be able to safeguard the fertility of young cancer patients who would otherwise be left sterile after their cancer treatment. However, some restraint in portraying this option as young girls' only option is in order. Whereas this is the truth for those girls at a high risk of sterility, it is not for a significant group of patients who have a low to medium risk of infertility before reaching reproductive age. For this group, the ruling paradigm that they can either choose to cryopreserve prepubertal ovarian tissue with no guarantee of future benefit or do nothing and hope that they will still be fertile by the time they want to reproduce, is incomplete. A possible third option that should be included and presented to young patients, is the possibility to come back to the clinic once they reach adolescence, test their ovarian reserve and if needed and desired, cryopreserve oocytes (or ovarian tissue for that matter) at that time. For sure, the ethical superiority of this third option will depend on the clinical outcomes of both procedures, which are both uncertain at this time. Yet, the sheer absence of this third option in the existing literature on fertility preservation options, and thus probably also in the possibilities offered to patients, is remarkable and needs to be addressed.

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H.M. wrote the commentary.

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