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DEBATE

Social sperm freezing

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Increased paternal age has been associated with lower fertility and higher genetic risk for the offspring. One way to prevent these consequences is to freeze sperm at a young age. Social sperm freezing could be developed in a way similar to social oocyte freezing. The main difference between freezing oocytes and sperm is that social sperm freezing is much less focussed on fertility preservation and much more on avoiding increased genetic risk. Contrary to what some people seem to believe, sperm freezing is more complicated than it looks at first sight. This article considers three practical aspects: freezing, storage and testing. It is concluded that the remedy (cryopreservation) may itself cause damage to the quality of the spermatozoon and to its genetic integrity, thus undoing the possible benefits in terms of fertility and health of offspring.

Key word: andrology / IUI / male infertility / semen analysis

Introduction

Men tend to postpone family building. Over the last 45 years, the mean age of first time fathers has increased in the USA from 27.4 to 30.9 (Khandwala *et al.*, 2017). The postponement of the family project has been linked to a series of changes: the increased status of women, greater gender equity, the rise of individualism as opposed to traditional family norms and the importance of higher education especially for women (Couture *et al.*, 2020). Economic factors such as the lack of supportive family–work balance policies and the inaccessibility of the housing market for young couples may also play a role. The latter factors are related to individual and interpersonal dynamics. Men, like women, may also postpone family building until they feel that their social, psychological and material situation is stable (Thompson and Lee, 2011).

Several possible reactions to this trend are possible. One could start campaigns to make men aware of their 'biological clock' or introduce changes in society to facilitate the combination of private life and work. One solution that has attracted attention was to bank sperm at a young age for use at a more advanced age (Gromoll, 2015; Hudson, 2015; Smith, 2015; Hens, 2017; Jennings *et al.*, 2017; Phillips *et al.*, 2019). This solution can, analogous to the trend in women, be called 'social sperm freezing'.

Social freezing?

An important point in this debate is which instances of sperm freezing should be labelled 'social' sperm freezing. In the context of oocyte freezing, this is a notoriously difficult question (Pennings, 2013). This decision is more than mere semantics since the label determines in many countries whether the intervention will be reimbursed by health insurance. Cancer patients and people with Klinefelter syndrome will probably be labelled medical freezing because of the presence of a medical condition. However, if this criterion is adopted to discriminate between social and medical, sperm freezing should also be offered to obese men since obesity is also a medical condition which affects sperm quality (Du Plessis *et al.*, 2010). To add an extra layer of complexity, what about men planning sex reassignment surgery? Leaving the criteria aside for a moment, there seems to be little doubt that sperm freezing to prevent age-related fertility decline will be labelled 'social' freezing.

Other groups for which sperm freezing might be useful would be certain professions such as firefighters, farmers and soldiers (Ravitsky and Kimmins, 2019). Still, there are few data on how much their fertility is affected and for how long. One Danish cohort study found an increase in risk among full-time firefighters (Petersen *et al.*, 2019). The risk for military men seems to be fairly limited (Martini and Doyle, 2019).

The best documented application of social freezing is freezing before vasectomy. Vasectomy is used as a contraceptive method by approximately 5% of married men, which results in 40–60 million men worldwide (Schwingl and Guess, 2000). More than 500 000 vasectomies are performed in the USA annually (Sharma *et al.*, 2013). Vasectomy renders a man sterile. Although the intervention should be considered as permanent, about 20% of vasectomised men desire future children

(Sharma et al., 2013). About 6% decide to undergo vasectomy reversal (Brannigan, 2012) and approximately 50% of these men will be able to achieve spontaneous pregnancy after the operation (Majzoub et al., 2017). If all men banked sperm before the vasectomy, the 20% with the wish for a child would probably use their frozen sperm, thus avoiding a reversal operation (with limited success) or a testicular sperm extraction (TESE) followed by an IVF/ICSI procedure (also with limited success). Sperm banking might be cost-effective for vasectomised men because of their sterility, renewed wish for a child and utilisation rate. Still, already for this small subsection of the male population, large numbers are involved (depending on the country).

At the moment, few men are freezing their sperm for age-related reasons but there is anecdotal evidence that the demand is growing (Hudson, 2015). Although it is difficult to speculate about the future, it does not seem farfetched to predict that, when the message about the male biological clock is spread, more men will bank their sperm. Studies indicate a general lack of awareness among men about the effect of age on fertility and child health (Daniluk and Koert, 2013; Hammarberg et al., 2017). Some players (clinics, sperm banks) may also tend to overstress the advantages of freezing because of financial interests in sperm banking. Still, there are reasons to doubt a speedy uptake. A strong deterring factor is men's view on reproductive masculinity (Daniels, 2006). This concept includes that men are less vulnerable to reproductive harm than women and are distant from health problems to their children (Daniels, 2006). In addition, even when men accept the existence of age-related fertility decline, they do not see it as related to their own personal lives (Law, 2020). This view, in combination with the practical elements discussed in this article, make it highly unlikely that men will be queuing to freeze their sperm any time soon.

Reasons to freeze

Two important effects of increasing paternal age are discussed in the literature: declining fertility and increasing genetic risk. These effects are also possible reasons for sperm banking. There is evidence (be it not equivocal) that sperm quality decreases with age. Fecundity in men >35 years is 50% lower than in men >25 years. There is a steady decline for all semen parameters by age but no cut-off point can be determined (Ramasamy et al., 2015; Halvaei et al., 2020). As a consequence, time to pregnancy increases gradually with paternal age (Phillips et al., 2019). Paternal aging has been shown to correlate with sperm DNA breaks (Belloc et al., 2014; Carlini et al., 2017). Advanced paternal age (>40 years) is associated with accumulated damage to sperm DNA subsequently causing numerical and structural abnormalities in sperm chromosomes, single gene mutations and increased sperm DNA fragmentation (3% per year of age) (Yatsenko and Turek, 2018). The DNA Fragmentation Index (DFI) has been shown to be a valuable tool for prediction of fertility *in vivo* (natural conception and IUI). A high DFI (>30%) is also associated with lower fertilisation rates in IVF and ICSI although the available literature for ICSI is still undecided (Cissen et al., 2016; Oleszczuk et al., 2016; Simon et al., 2017). In addition, increased paternal age is also associated with an increase in pregnancy-associated complications such as miscarriage rate, pre-eclampsia, preterm births and surgical deliveries (Sartorius and Nieschlag, 2010).

However, an important difference between men and women regarding fertility decline is that for women the decline reaches the bottom by age 50 while the decline for men only goes down to zero in their 7th or 8th decade of life (de Brucker and Tournaye, 2014). That fact removes much of the urgency and usefulness of storage. The term 'biological clock' thus has a different meaning for men than for women. Nevertheless, it is important to stress the effect of age on fertility since this male factor contributes to the couple's infertility (Turner et al., 2020).

Besides reduced fertility, studies have shown a correlation between paternal age and a multitude of disorders such as autism, schizophrenia and other forms of psychiatric morbidity (Couture et al., 2020). The almost exclusive attribution of responsibility for the future child's health to the woman in both the academic and lay literature is clearly gender biased (Hens, 2017). Still, the diseases for which a correlation has been demonstrated with paternal age are rare and a significant increase in multiple very rare diseases only results in a small total increase of genetic risk (Gromoll et al., 2015; Oldereid et al., 2018). Whether a high DFI also leads to more disorders in offspring is still unknown although some studies have found a pronounced effect on child morbidity as a result of older parental age, possibly caused by sperm DNA damage (Bergh et al., 2019).

The conclusion from the main effects of paternal age is that, contrary to social oocyte freezing, social sperm freezing is much less focussed on fertility preservation and much more on avoiding increased genetic risk. This focus considerably lowers the benefits of freezing. The general evaluation of social sperm freezing will depend on whether or not one judges the increased genetic risks as significant.

Practical issues

Many people seem to assume that sperm freezing is very simple: a man goes to a clinic, masturbates and the sperm sample is frozen. However, things are more complicated. We will consider three parts of the process, freezing, storage and testing, as well as cost issues.

Sperm freezing

Freezing sperm has a negative effect on all sperm parameters. Freeze-thawing is harmful for the spermatozoa as it causes an important reduction of viability and motility (Nijs and Ombelet, 2001) as well as structural damage to the mitochondria and cell membranes, leading to adverse effects on sperm function (Paoli et al., 2014). There is evidence that cryopreservation is associated with DNA fragmentation and DNA single-stranded breaks in sperm (Jennings et al., 2017; Le et al., 2019). Sperm cryopreservation negatively affects sperm DNA integrity and has a negative correlation with sperm basic parameters (motility, morphology and viability) (Lusignan et al., 2018). In a comparative analysis, five different cryopreservation media had negative effects on sperm motility and morphology (Raad et al., 2018). This study clearly showed that the recovery rate of competent spermatozoa after cryopreservation is still critical in infertile men and therefore that frozen semen samples should be used only when necessary. According to Tvrdá et al. (2020) examining semen samples from 50 donors with a normal spermiogram, exposure of spermatozoa to low temperatures, independent of the chosen freezing protocol, leads to a

higher susceptibility to sperm DNA damage. This damage is lower following vitrification in comparison to traditional cryopreservation. Sperm freezing prior to swim-up selection is likely to achieve better outcomes after thawing, especially in patients presenting a poor sperm baseline (Palomar Rios *et al.*, 2018).

Studies attempting to explain the mechanisms responsible for cryopreservation-induced DNA damage in sperm are still limited. Some have reported an increase in sperm with activated caspases after cryopreservation while others have found an increase in the amount of oxidative DNA damage (Paoli *et al.*, 2019).

Various factors involved in the freezing process, including sudden temperature changes, ice formation and osmotic stress, have been proposed as reasons for poor post-thaw sperm quality (Amidi *et al.*, 2016; Hezavehei *et al.*, 2018). There is an increased risk of formation of intracellular ice crystals during the thawing phase, which can lead to irreversible cell damage (Paoli *et al.*, 2014). Additionally, little is known regarding the more-recently discussed aspects of sperm cryobiology, such as the possible epigenetic and proteomic modulation of sperm and trans-generational effects of sperm freezing (Hezavehei *et al.*, 2018). Animal studies on boars have shown that epigenetic modifications may occur in sperm cells during the freezing process (Flores *et al.*, 2011; Zeng *et al.*, 2014).

Another possible consequence of sperm freezing is an increasing number of IVF/ICSI cycles. If the sperm quantity and quality after thawing is good enough for IUI, the cost is limited. If this is not the case, and one believes that the genetic risk reduction is sufficiently important to use the frozen semen, a higher number of IVF/ICSI cycles will be performed than would be the case without freezing. This not only means an additional cost for the patient or the health services, but it also puts a heavy burden on the shoulders of the female partner (Ravitsky and Kimmins, 2019). As Turner *et al.* (2020) states: 'Male infertility is a women's health issue', and so is male postponement of reproduction. Moreover, the use of IVF/ICSI increases the health risk for future offspring. The perinatal outcome for babies born after assisted reproduction is worse than that for babies born after natural conception (Pinborg *et al.*, 2013; Berntsen *et al.*, 2019; Zhao *et al.*, 2020). Non-IVF pregnancies (IUI or ovarian stimulation with timed intercourse) have a better perinatal prognosis than IVF/ICSI pregnancies but it is still worse than that of natural conception pregnancies (Ombelet *et al.*, 2016). Children born after ART have altered epigenetic profiles and these alterations may be one of the key areas to explore in the future (Berntsen *et al.*, 2019). These are enough reasons to avoid ART if it is not needed.

Given these facts, it is not at all clear that freezing would reduce the total genetic risk, as the freezing process itself may increase the genetic risk for the offspring. So the gain in genetic risk reduction as a consequence of using younger (frozen) sperm might be outdone by the loss in genetic integrity as a consequence of cryopreservation.

Sperm storage

Freezing sperm implies that tests should be performed on the donor. The European Tissues and Cells Directive 2004/23/EC obliges clinics to test all samples for infectious diseases before storage to prevent cross-contamination of samples. Men who intend to freeze should be informed about these tests and about the possible findings. In addition, a contract should be made that stipulates what should be done with the samples in case of death or non-use. The maximum storage period should also be determined either by the clinic or the regulatory system. The present debate in the UK on the statutory limit of 10 years demonstrates the relevance of this issue (Progress Educational Trust, 2020). Moreover, the question should be raised of whether the samples can be donated to a third party if the provider decides not to use them for himself. If so, additional counselling and genetic screening would be necessary. Depending on the possible options, quite extensive counselling would be needed to ensure informed consent by candidate freezers. Other practical aspects include the fee for storage which may be important especially if the sperm has to be stored for decades. A quick search on the internet shows that the fee for the initial consultation, blood testing and sperm processing and analysis is between $1000 and $1400. The annual storage fees are somewhere between $150 and $450, depending on the number of ejaculates stored and the duration of storage. Given these amounts, contracts should also indicate what will be done with the sperm in case of non-payment of the storage fee. Finally, there is the cost of several rounds of IUI when the man decides to return for his sperm. The cumulative clinical pregnancy rate after three cycles of IUI is 18%, which increases to 30 and 41% after six and nine cycles, respectively (Cohlen *et al.*, 2018). So a relatively large number of IUI cycles will be needed while success will still be limited.

Sperm testing

An important question is whether sperm quality should be tested before freezing. Contrary to oocytes, sperm quality can be checked to a certain extent. The current measurement of sperm parameters does not allow a determination of whether a man is fertile or infertile. The parameters (with the obvious exception of azoospermia) can merely serve as a guide (Oehninger and Ombelet, 2019). The quality check may be important to decide how many samples should be stored in order to have a reasonable chance of a pregnancy with IUI. All men should receive an explanation of the procedure and be counselled about the risks and benefits. This includes the fact that the test may reveal that the man is azoospermic since this applies to about 1% of the male population (Ombelet *et al.*, 1997). Semen analysis may also show a low sperm count. Men with a low sperm count should be advised to store more samples to allow insemination later. Moreover, testing the fresh sample should be followed by a post-thaw test, since in general sperm quality is negatively affected by freezing. In a study by the British Fertility Society Working party on sperm donation services in the UK (2008), 54.5% of potential sperm donors were rejected at the semen analysis stage. Part of that percentage was due to post-thaw quality. Moreover, sperm testing may create negative psychological effects (anxiety) in many men unnecessarily. Information that a man's sperm quality is low may have a negative impact on his self-esteem and masculine status, even when he is told that this does not have implications for natural conception (Hanna and Gough, 2020).

An interesting 'incidental finding' of testing is an increased health risk. Semen quality is a marker for men's general health. Some authors have proposed an annual physical examination of men that includes semen analysis, since male reproductive health assessment can lead to early detection of potential chronic disease and cancer (Choy and Eisenberg, 2018; De Jonge and Barratt, 2019). Semen quality is associated with long-term morbidity and a significantly higher risk of

hospitalisation, particularly for cardiovascular diseases and diabetes mellitus (Latif et al., 2017). Men considering freezing should know that sperm testing may reveal a serious health problem. At the same time, this information may be an extra reason to perform testing.

Reimbursement and organisation

There has been a heated debate on whether or not cryopreservation of oocytes should be reimbursed by national health insurance (Mertes and Pennings, 2012). A similar debate has already started for sperm freezing. One reason to reimburse sperm but not oocytes could be that the whole process is simpler and cheaper. As mentioned above, the total cost may still be around 4000€ when multiple samples are stored for 10 years or more. Public funding raises the question of justice: access to freezing would be limited when people have to pay out of pocket. Smith (2015) therefore proposed state-funded infrastructure to guarantee access for all. Freezing could also be offered as a premium insurance service (Hudson, 2015). An important element would be how many men would decide to freeze their sperm. Pacey calculated for the UK that if 50% of the men who turn 18 would come forward, the total cost would be £79 million per year for the National Health Services (Pacey, 2015). This percentage most certainly is a gross overestimation of the actual number of men who would want to freeze their sperm but it highlights the possible burden on the health insurance system. Given the limited health care budget, it is hard to justify spending large sums on sperm banking.

An important issue to decide on public funding is cost-effectiveness. Cost-effectiveness will, amongst other variables, be determined by the utilisation rate. The younger the man is when he freezes, the less likely that he will return to use his sperm. Moreover, the fact that the man will still be fertile when he is 40 or 50 is a strong argument against both freezing and later use of the frozen sperm. The use of frozen sperm also necessarily implies the medicalisation of reproduction with everything connected to that: loss of control, investment of time and money, and loss of privacy.

Scenarios

Let us take a closer look at the most likely scenarios. First, a 25-year-old man intends to spend the next 20 years of his life building a career. He believes that raising a child during this period would seriously hamper his chances of reaching this goal. Moreover, he would not be able to function as the kind of father he wants to be. Should he be advised to freeze his sperm? How high are the chances of him using his frozen sperm later rather than try for natural conception when he is ready to have a child? His fertility will have gone down compared to when he was younger but will his fresh (older) semen be worse than his frozen (younger) semen?

Consider a second retrospective scenario: a 45-year-old man has frozen his sperm when he was 25. He is now ready to start a family. Should we advise him to use his frozen sperm? It seems that a case could be made for their use on the condition that the sperm samples allow IUI. The costs of freezing have been made and non-use would come down to a complete waste of both the sperm and investment. The cost of IUI should be balanced against the benefit of genetic risk reduction (assuming that there is indeed a risk reduction). When the sperm is unsuitable for insemination (because of limited volume or quality), the balance shifts considerably. It seems unreasonable to argue that IVF/ICSI is justified by the small risk reduction. It would be a heavy price to pay by his partner. In addition, the use of IVF and ICSI itself may increase the risk of health problems for the offspring and thus annihilate the benefit. This point is also related to the question of whether older men (>45) should be offered or recommended to have prenatal genetic screening (Hens, 2017; Brandt et al., 2019). Most people seem to believe that the risk is too small for such measures.

Sperm donors and others

At the moment, fertility specialists and fertility clinics do not offer or recommend sperm freezing to males of advanced age to avoid increased genetic risk. However, the same genetic risk is used to justify an age limit for sperm donors. At present, most countries opt for an age limit of 40 or 45. A notable exception is Canada where in a recent report no maximum age for donors was set (Health Canada, 2020). In the UK, the age limit went up from 41 in the 8th Code of Practice of the Human Fertilisation and Embryology Authority to 46 in the 9th Code of Practice, a move probably motivated by the shortage of donors.

The age limit for sperm donors is justified by the increased genetic risk related to age and the declining sperm quality. The declining sperm quality would lower the success rate. Some sperm banks have even lowered the upper age limit to 35 in order to maximise success rates (Kay and Barratt, 2011). Recipients are buying a service and are expecting a high-quality sperm sample. Obviously, a balance will have to be found between a sufficient number of donors and sperm quality. While a male partner can try many times without additional cost, recipients of donor sperm want to become pregnant with a limited number of inseminations. Lowering the threshold for sperm quality would increase the time to pregnancy and the costs. The latter problem could be solved by making sperm of lower quality cheaper. Sperm of men younger than 35 could be made more expensive than sperm of older men. At present, some sperm banks already charge different fees according to the quality of the sperm (Koustas et al., 2020). Recipients must be informed about the disadvantages of sperm from older men but the choice would be up to them. People who opt for a known donor who is above the age limit make the same choice. If the success rate would be the sole difference, the reasoning above might be acceptable, but this solution becomes harder to defend when we consider genetic risks. Rich recipients can afford to buy first quality sperm with a lower chance of genetic abnormalities in their children while poor recipients cannot. A similar reasoning would apply when people can opt for a donor who has undergone expanded carrier screening and one who has not undergone screening. As long as these risks are below a societally fixed threshold, such arrangements would be acceptable. Still, one should realise that such differential pricing leads to the increasing commercialisation of the donation practice.

Conclusion

Freezing sperm for age-related reasons is unlikely to be proportional to the benefits mainly because of the limited effect of aging on male

fertility. The increase in genetic risk with age is also generally considered as limited. Moreover, the remedy (cryopreservation) may itself cause damage to the quality of the sperm and the genetic integrity. Nevertheless, the effects of paternal aging on the health of the offspring and on men's fertility is sufficient to at least inform the population about these effects. Postponing fatherhood has its consequences just like postponing motherhood.

Data availability

No new data were generated or analysed in support of this research.

Authors' roles

G.P. proposed the original idea. G.P., V.C. and W.O. developed the arguments, searched the literature and participated in writing the paper.

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