REVIEW ARTICLE

Fertility Preservation for Non-Medical Reasons

Controversial, but Increasingly Common

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SUMMARY

Background: Fertility-preserving measures for women are increasingly being performed for non-medical reasons in Germany. This is now a controversial matter.

Methods: The authors searched the PubMed database for pertinent publications on the basis of their clinical and scientific experience and evaluated relevant data from the registry of the German FertiPROTEKT network (www.fertiprotekt.com). The various fertility-preserving measures that are available are described and critically discussed.

Results: In most cases, the creation of a fertility reserve currently involves the cryopreservation of unfertilized oocytes, rather than of ovarian tissue. Most of the women who decide to undergo this procedure are over 35 years old. According to data from the FertiPROTEKT registry, most such procedures carried out in the years 2012 and 2013 involved a single stimulation cycle. The theoretical probability of childbirth per stimulation is 40% in women under age 35 and 30% in women aged 35 to 39. If the oocytes are kept for use at a later date, rather than at once, the maternal risk is higher, because the mother is older during pregnancy. The risk to the child may be higher as well because of the need for in vitro fertilization (IVF). Pregnancy over age 40 often leads to complications such as gestational diabetes and pre-eclampsia. IVF may be associated with a higher risk of epigenetic abnormalities. Ethicists have upheld women's reproductive freedom while pointing out that so-called social freezing merely postpones social problems, rather than solving them.

Conclusion: Fertility preservation for non-medical reasons should be critically discussed, and decisions should be made on a case-by-case basis.

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Thanks to advances in reproductive medicine and reproductive biology, oocytes can now be harvested by means of gonadotropin stimulation with minimal risk (<1%) of hyperstimulation and unfertilized oocytes can be cryopreserved. In recent years these techniques have been used for medically indicated preservation of fertility, e.g., in women undergoing chemotherapy or radiotherapy (1, 2). Once the medical indications were confirmed, it was only a short step to the use of the same techniques for non-medical reasons. This kind of intervention—often referred to as "social freezing"—is of a quite different dimension than medically indicated cryopreservation or "medical freezing". In the case of medical indications, emergency measures are taken to preserve fertility in the event of loss of gonadal function owing to cytotoxic treatment. In non-medical indications the woman concerned wishes to postpone pregnancy and childbirth, perhaps for career reasons or because she does not currently have a partner. Although medical freezing and social freezing cannot always be clearly distinguished, the risks of fertility-preserving measures as well as their efficacy have to be evaluated from the medical and ethical viewpoints.

Techniques

Both ovarian tissue and unfertilized oocytes can be preserved. If the woman is in a stable relationship, fertilized oocytes in the form of zygotes or embryos can be placed in storage.

To date, cryopreservation of ovarian tissue has been limited to women scheduled for cytotoxic treatment. Usually 50% of an ovary is removed laparoscopically, stored in liquid or gaseous nitrogen, and, in the event of loss of ovarian function, transplanted into the remaining ovaries or the pelvic wall (3–5).

The success rate is hard to quantify. With adherence to proper procedures, however, 20 to 30% of transplantations are followed by successful childbirth, provided the tissue was removed before the woman reached the age of 35 years (5). It can be assumed that the success rate will be still higher in future due to new developments and the long time for which the tissue survives after transplantation.

The dangers lie in the outpatient laparoscopy procedures that are necessary for tissue removal and

TABLE 1

Theoretical likelihood of giving birth after social freezing*1

Age at cryopreservation	Number of cryopreserved oocytes/stimulation (mean ± SD)	Number of cryopreserved oocytes/patient/year (mean ± SD)	Anticipated estimated number of transferable embryos per stimulation*2	Anticipated estimated birth rate per stimulation (circa)*3
<35 years	11.1 ± 6.5	11.4 ± 6.1	3.3	40%
35–39 years	8.7 ± 7.3	11.1 ± 8.3	2.6	30%
40–44 years	9.1 ± 8.3	9.7 ± 8.8	2.7	15%

SD, standard deviation

*1 Calculation based on overall number of oocytes per stimulation and woman in the FertiPROTEKT registry for 2013

*2 Rate of fertilized oocytes after thawing and fertilization: 44% (according to *Table 3*: 63.1% × 70.1% = 44%). Rate of embryos from fertilized oocytes: 67% (FIVNAT: Annual report 2011. www.sgrm.org/wb/pages/de/fivnat-kommission/jahresberichte.php); rate of embryos per thawed oocyte: 29.5% (44% × 67% = 29.5%).

*3 Estimated according to Garrido et al. 2011 (12). The calculations are based on the assumption that the developmental potential of embryos from „fresh" oocytes and those generated from cryopreserved oocytes is comparable. Note that the birth rate does not increase linearly with the number of stimulation cycles because the success curve sinks increasingly after cumulative transfer of five embryos.

retransplantation. The complication rate is <1% (6). Since spontaneous pregnancy is possible following retransplantation, there is probably no risk of the epigenetic changes that have been proposed as potential complications of in-vitro fertilization (IVF) (7, 8). Furthermore, the tissue can be retransplanted to postpone the menopause. This is currently being explored as a new option.

To date, however, only oocytes, not ovarian tissue, are used for social freezing. Oocytes can be retrieved by a stimulation process corresponding to that during IVF. Vitrification, a new freezing technique, enables preservation of cryosensitive oocytes—with high survival rates (9).

When the time comes for the oocytes to be used, they have to be thawed out, fertilized, and transferred in the embryonal stage. Intracytoplasmic sperm injection (ICSI) is often required for fertilization of the thawed-out cells.

The costs of stimulation treatment, retrieval of oocytes, and the necessary medications amount to ca. € 3000 to 4000, including cryopreservation and storage of the oocytes. The actual sum varies according to drug consumption and other factors. If the oocytes are then used, there are additional costs of ca. € 2000—depending on the number of oocytes thawed out and treated—for ICSI and the transfer cycle (10).

The success rates depend greatly on the number of cells harvested, on the woman's age at the time of removal, and on the expertise of the center where cryopreservation takes place. Highly specialized facilities achieve pregnancy rates after cryopreservation by the vitrification process that are comparable with the results of embryo transfer without foregoing cryopreservation (9). It is unclear, however, whether these success rates are transferable to all fertility centers.

Table 1 shows the number of oocytes retrieved per stimulation cycle in three age groups according to the registry of the FertiPROTEKT network (www.fertiprotekt.com) (11), with the anticipated birth rates. A second cycle of stimulation doubles the number of embryos transferred but not the chance of success; the latter rises increasingly slowly with the cumulative transfer of more than five embryos (12).

Characteristics of the patients

Results from the international literature cannot simply be extrapolated to Germany, because cultural and economic factors play a role. Interestingly, however, data from other industrialized countries such as the USA (13) and Belgium (14) are similar to those from the FertiPROTEKT registry, which includes centers in Germany, Austria, and parts of Switzerland.

What is clear is that the number of women opting for fertility preservation increased in 2013. Although the FertiPROTEKT registry does not cover all treatments carried out in Germany, because not all German IVF centers have joined the FertiPROTEKT network, a trend can be discerned. While in 2012, 30 women were counseled and 22 treatments were carried out as a result, in 2013 these figures increased to 190 and 134 respectively.

As shown in *Table 2*, the women treated in 2013 were predominantly graduates and half of them were in the age group 35 to 39 years. The majority had only one cycle of treatment in this period. Some of the women were in a stable relationship or even had one or more children.

Efficacy and safety of oocyte cryopreservation and storage

The cryopreservation of unfertilized oocytes has long been a routine procedure, e.g., to preserve fertility in advance of oncological treatment or, in other countries, in oocyte donation programs. The efficacy of cryopreservation for medical and non-medical indications is comparable (15). The fact that the relevant professional associations in the USA published a guideline on cryopreservation of mature oocytes in 2013 can be interpreted as an expression of general acceptance. The authors of this document state that cryopreservation of unfertilized oocytes should no longer be deemed

experimental; in contrast, it can now be considered routine, because there is no evidence of higher rates of chromosomal aberrations, malformations, or developmental deficits (16). The equivalent European society also has no reservations regarding cryopreservation of oocytes for non-medical indications, but recommends exhaustive counseling (17).

The country with the most extensive experience of the freezing of unfertilized oocytes is Italy, where, until 2009, the law governing IVF programs stipulated that only oocytes destined for transfer could be fertilized. All excess cells had to be cryopreserved unfertilized on the day of collection (18) *(Table 3)*.

Cil and colleagues (19) estimated the age-related reduction in live birth rate after transfer of cryopreserved oocytes on the basis of the data from ten studies. They showed that the rate decreased steadily between the ages of 25 and 42. Their findings roughly corresponded with our own calculations in *Table 1*, although the latter include the average number of oocytes harvested. The study reinforces the point that cryopreservation should be carried out before the woman reaches 35—particularly since the number of oocytes that can be harvested goes down with the age-related decrease in the ovarian reserves.

The use of reproductive medicine techniques without a medical indication demands careful consideration of the potential complications.

The principal risks are hemorrhage and/or injury during follicular aspiration and severe hyperstimulation syndrome. The annual statistics of the German IVF registry for 2013 show an overall complication rate of 0.8% and occurrence of severe hyperstimulation syndrome in 0.25% of cases (20). The latter can—as recommended in the FertiPROTEKT statement on social freezing (21)—be reduced to practically 0% with a GnRH agonist (22).

The risks associated with fertility preservation for non-medical reasons are therefore limited, but must always be described during the counseling process.

The data on long-term storage of vitrified oocytes are still sketchy. Pregnancies have been achieved after storage for several years, but the risks cannot yet be assessed.

Before cryopreserved oocytes can be used for a pregnancy, they must first be thawed out and fertilized in vitro. One important factor in the debate on social freezing is the danger of malformation for the child. According to the results of a large Australian study in which the authors investigated 6163 IVF children in an overall cohort of 308 974 children, assisted reproduction techniques are associated with an elevated risk of malformation (multivariate adjusted odds ratio [OR] 1.28; 95% confidence interval [95% CI] 1.16 to 1.41). The malformation rate was 8.3% following IVF, compared with 5.8% after spontaneous conception (23).

Furthermore, a Swedish registry analysis of >2.5 million births revealed significantly higher proportions of children with autism (OR 1.14, 95% CI 0.94 to 1.39) and mental retardation (OR 1.18, 95% CI 1.01 to 1.36) for IVF pregnancies than for spontaneous pregnancies (24). The difference is low in absolute terms, however; the prevalence of autism and mental retardation in pregnancies resulting from spontaneous conception was only 15.6 and 39.8 per 100 000 person years respectively. Judging from the calculated OR, the absolute numbers for IVF pregnancies can only have been ca. 10% higher.

Ultimately it remains to be ascertained whether these changes are genuinely due to IVF treatment, since infertility with or without assisted reproduction techniques is related with an elevated risk of malformation (23).

However, new studies show that functional organic changes resulting from epigenetic changes could also be associated with IVF per se. Changes in vascular function of the kind seen in type 1 diabetes have been demonstrated by Scherrer et al. in IVF children (7) and by Rexhaj and colleagues in a mouse model (8). According to the authors these findings are most likely related to IVF-induced epigenetic changes.

Therefore it is at least conceivable that IVF with cryopreserved oocytes could elevate the risk for the child even in healthy and presumably fertile women.

TABLE 2

Characteristics of the women treated and the results of their treatment[*1]

Women treated (n)	134
Age <35 years, n (%)	35 (26.1%)
Age 35–39 years, n (%)	68 (50.8%)
Age ≥ 40 years, n (%)	31 (23.1%)
Graduates[*2], n (%)	81/106 (76.4%)
Already with own children[*2], n (%)	3/79 (3.8%)
In a relationship[*2], n (%)	23/117 (19.7%)
1 stimulation cycle performed, n (%)	99 (73.9%)
2 stimulation cycles performed, n (%)	29 (21.6%)
3 stimulation cycles performed, n (%)	5 (3.7%)
4 stimulation cycles performed, n (%)	1 (0.8%)
Oocytes/overall treatment <10, n (%)	70 (52.2%)
Oocytes/overall treatment 10–20, n (%)	45 (33.6%)
Oocytes/overall treatment >20, n (%)	19 (14.2%)
Stimulation cycles (n)	**176**
Oocytes/stimulation cycles <5, n (%)	49 (27.8%)
Oocytes/stimulation cycles 5–10, n (%)	51 (29.0%)
Oocytes/stimulation cycles >10, n (%)	76 (41.2%)

[*1] Based on the women treated in 2013; results according to the FertiPROTEKT registry
[*2] Data not available for all of the 134 treated women

Legal aspects

In Germany there are no legal restrictions regarding fertility preservation measures and no age limit for embryo transfer. Theoretically, therefore, it would be

TABLE 3

Results of cryopreservation of unfertilized oocytes*

	Slow freezing	Vitrification	p
Cycles (n)	8927	5 401	–
Survival rate per thawed oocyte	51.1%	63.1%	Significant
Fertilization rate per oocyte	71.6%	70.1%	Not significant
Pregnancy rate per cycle	12.0%	14.4%	Significant
Pregnancy rate per transfer	14.8%	18.0%	Significant
Implantation rate per thawed oocyte	8.1%	9.5%	Significant
Children born (n)	778	560	–
Malformation rate	0.5%	1.3%	Not significant

n, Number; $p<0.05$
* Data for Italy 2007–2011 (13) (without adjustment for age of women etc.)

BOX

Potential advantages and disadvantages of social freezing*

- **Advantages**
  - Childbirth is postponed to a later time.
  - The cryopreserved oocytes may increase the likelihood of conception in the event of later occurrence of fertility-reducing diseases such as premature ovarian failure or endometriosis.
  - The egg cells used to achieve conception were harvested when the woman was younger and may thus be subject to a lower risk of chromosomal malformations such as Down syndrome.
- **Disadvantages**
  - High probability of birth only with multiple stimulations and oocyte cryopreservation before the age of 35
  - High costs for every stimulation, oocyte retrieval, and cryopreservation procedure; for each year of storage; and for subsequent in-vitro fertilization (IVF) of the oocytes and embryo transfer
  - Increased risk of multiple pregnancy due to the customary transfer of two embryos at a time and therefore higher rate of pregnancy complications
  - Elevated risk of complications such as pre-eclampsia and gestational diabetes in women > ca. 40 years of age
  - Lack of clarity with regard to the danger of epigenetic changes and other malformation risks due to the necessary IVF procedure

*Defined here as cryopreservation of unfertilized oocytes

possible to transfer embryos to postmenopausal women.

Because no legal age limit exists, FertiPROTEKT has attempted to establish voluntary self-regulation in all centers where social freezing is offered (21). Given that the average age for onset of menopause is 50, FertiPROTEKT recommends that embryo transfer should take place before the beginning of the woman's 50th year of life. There is no guarantee that centers will follow this recommendation, however, and in any case every woman has the right to receive her oocytes and take them to another center or country where no age restriction applies.

Ethical aspects

The ethical dimension of social freezing is undoubtedly complex and multifaceted.

Ethicists see a woman's autonomy as an essential good by reason of which she can decide for herself whether she takes measures for fertility preservation (25). The same argument was advanced when oral contraception was introduced and again when IVF became possible. Given that these two forms of treatment have become broadly accepted from the ethical viewpoint, ethicists take the view that it would be contradictory to condemn social freezing as ethically unacceptable across the board. Moreover, it is pointed out that social and medical reasons for cryopreservation of oocytes often cannot be clearly distinguished. For example, the threat of reduced fertility at a higher age can be interpreted as a medical indication (26).

Nevertheless, social freezing should be considered from all sides. Only the woman's own health is risked by the measures required for preservation of unfertilized egg cells, but if the oocytes are subsequently used to achieve pregnancy she is also responsible for the health risks to the child, because both IVF and pregnancy at a higher age are associated with greater danger for the fetus. Furthermore, statement 22/2013 of the Swiss National Advisory Commission on Biomedical Ethics (27) notes that the preservation of one's oocytes does

not solve the problems of finding a partner or achieving the best balance between work and family life. There has been no discussion to date of what should be done with oocytes, particularly fertilized oocytes in the form of zygotes and embryos, that are not used for pregnancy. The options include donation to sterile couples, use for research purposes, and destruction.

Whether oocyte donations will be reduced by social freezing cannot yet be judged. Possibly, however, oocyte donation will actually increase, because women will rely on their cryopreserved oocytes but in most cases no birth will result *(Table 1)*.

The perspective for obstetricians

One essential problem of fertility preservation is the possibility of pregnancy at a greater age. Obstetricians are already confronted with this problem because of the increasing number of oocyte donations in other countries. In many countries the maximum age for receiving an embryo transfer after oocyte donation is set at around 50 years, but in some places even this high limit is exceeded.

Compared with gestation at the age of 20 to 30 years, single pregnancy at 50 is associated with a sixfold risk of gestational diabetes (6%) and a fourfold chance of mild (14.4%) or severe (9%) pre-eclampsia (28).

Furthermore, it should be considered that IVF is associated with a higher rate of multiple pregnancies because usually more than one embryo is transferred. This leads to a higher risk of complications during pregnancy and thus greater risk to the children.

The increasing complication rates for both mother and child in gestation at a higher age and in multiple pregnancies, together with the probably higher complication rates for IVF and ICSI per se (29), confront medicine and society as a whole with additional challenges.

Conclusion

Advances in reproductive medicine now permit preservation of fertility for non-medical indications, particularly in the shape of cryopreservation of unfertilized oocytes. There are arguments for and against this "social freezing" *(Box)*. The realistic chances of success, the risks for mother and child, the postponed but not solved problem of finding a partner, and the difficulty in balancing work and family life make it essential to consider social freezing critically and weigh up the indications carefully in each individual case.

KEY MESSAGES

- It is now possible to take measures to preserve fertility for non-medical reasons.
- In most cases oocytes are harvested after ovarian stimulation treatment and preserved in an unfertilized state.
- If the oocytes are subsequently used to achieve pregnancy, women over 40 have a higher risk of complications and the necessary in-vitro fertilization may also increase the risk for the child.
- The efficacy of the techniques is limited, particularly with cryopreservation of oocytes from women aged 35 or over.
- Physicians should discuss fertility-preserving measures critically with any woman who requests them for non-medical indications; each individual case should be decided on its merits.

Conflict of interest statement

Prof. von Wolff was involved in the establishment of the FertiPROTEKT network, which collects and analyzes the registry data discussed in this article. He is a member of the steering committee of FertiPROTEKT.

Prof. Nawroth is a member of the steering committee of FertiPROTEKT. He has received reimbursement of travel costs from Merck Serono.

Dr. Germeyer is a member of the steering committee of FertiPROTEKT.

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