Fertility and Sterility
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The importance of patient selection to analyze IVF outcome with transplanted cryopreserved ovarian tissue

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April 20, 2020

We would like to submit our invited editorial on manuscript Fertil Steril 29512
"Reproductive outcomes after IVF treatment in a cohort of Danish women transplanted with cryopreserved ovarian tissue"

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Editorial on
Fertil Steril 29512
"Reproductive outcomes after IVF treatment in a cohort of Danish women transplanted with cryopreserved ovarian tissue"

Title: The importance of patient selection to analyze IVF outcome with transplanted cryopreserved ovarian tissue

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Meeting the increasing demand for fertility preservation remains a challenge. Indeed, with increasing success of oncological treatments, offering fertility preservation before gonadotoxic treatment should be the standard of care. Hematologic and breast cancers represent the most frequent indications for fertility preservation, especially because they are cancers with the highest prevalence in the reproductive age group. Besides embryo cryopreservation and oocyte vitrification, ovarian tissue cryopreservation (OTT) is often proposed as fertility preservation option in specific indications such as prepubertal girls and women who cannot delay the onset of chemotherapy for ovarian stimulation.

The excellent outcomes of fertility preservation in general and ovarian tissue cryopreservation in particular have convinced oncologists to refer their patients to reproductive medicine specialists. Since its first implementation for cancer patients in 1996, followed by the first live birth in a Hodgkin's lymphoma patient in 2004, ovarian tissue cryopreservation is now accepted by ASRM as a fertility preservation option that is not experimental (1).

Ovarian tissue auto-transplantation has been performed worldwide, and after reimplantation of the frozen-thawed tissue into the pelvic cavity, ovarian activity is restored in over 95% of cases

(2). Pregnancies and live births with that technique have started to climb steadily, showing an exponential increase, with the number of live births as of June 2017 exceeding 130 (2) and probably more than 200 in 2020. Analyzing the percentage of transplanted patients in terms of success rate, 3 major centers (Sheba Medical center in Tel Aviv, Cliniques universitaires Saint Luc in Brussels and Infertility center in St Louis) report in 2020 in a series of 60 patients, a pregnancy rate of 50% and a live birth rate of 41% (3). These results prove the efficacy of the technique and support its use when fertility preservation is needed.

However, the success rates of OTT are not always reproducible, even within the same IVF units. The manuscript in this issue of F&S is proof of how important it is to carefully collect and analyze clinical data. (4) Skewed patient selection and incomplete data collection, may leave the readers with doubts on the efficacy of OTT. Indeed, one clear take home message from this work is the confirmation that ovarian tissue freezing is a robust option for some patients needing fertility preservation. In fact, the frozen tissue was cryopreserved (even if transported for up to 6 hours on ice), thawed and re-grafted successfully in all cases. However, what needs more caution is the interpretation of the IVF data for this cohort of Danish women.

The small number of patients advised to undergo IVF after OTT were highly heterogeneous. Indeed, two (cases 19 and 28) had whole body radiation requiring peritoneal OTT assuming ovarian atrophy, but there was no mention of possible impact on the uterus. In addition, some patients had already undergone IVF prior to the OTT, but these data were not presented, and 5 patients had elevated FSH levels already at the time of the first ovarian stimulation (therefore they were already very poor prognosis). Furthermore, 9 patients had no ovarian response at their first IVF and 4 underwent a second OTT before even doing the first IVF cycle. Finally, 2 of the patients that had the second OTT dropped out from additional IVF cycles and one wonders if they resumed their ovarian function and perhaps had a spontaneous pregnancy (assuming they were in the group of orthotopic ovarian grafting).

The authors provided no information on the steroid receptor status for 12/14 patients with breast cancer and similarly they had no information about follicular density on the histological samples prior to cryopreservation. This information may provide helpful in anticipating ovarian response and thus IVF outcome. It is unclear why oocyte freezing was not offered to the breast cancer patients. Indeed, oocyte freezing is recommended in these patients by American Society of Clinical Oncology (ASCO) guidelines of 2006, and later by ASRM, ESHRE and International Society for Fertility Preservation (ISFP) .

It becomes difficult to reconcile these poor IVF results of this study with the data that the same group has published extensively on this same topic in previous reports. Nonetheless, it is important to know that for certain selected patients as described here, OTT and subsequent IVF data cannot be extrapolated to the success rates known in literature. The high rate of pregnancy losses, some even in the second trimester, if confirmed from additional studies, requires proper patient counseling.

An interesting observation that certainly deserves more studies is the 36% empty follicle rate. This specific question has been previously reported. For example in a report from Belgium, the empty follicle rate was 29 %, and the fertilization rate of 50%. These patients were those that had not achieved spontaneous pregnancy after 1 year of menstrual cycling.

The possible causes of empty follicle syndrome were previously reported and include i) dysfunctional folliculogenesis due to elevated basal FSH concentrations during the early follicular phase, ii) asynchrony between granulosa cell maturation and oocyte maturation, and iii) damage to the oocyte itself by freezing, thawing and transplantation, leading to a higher rate of empty follicles or oocyte alterations, while granulosa cells may be more resistant.

In a recent systematic review by Andersen et al on ART outcomes in women transplanted with cryopreserved ovarian tissue the empty follicle rate varying between 23 and 35%, a fertilization rate of 57% (and particularly of 49% for the Danish cohort) and a live birth rate of 47,5% (19 women out of the 40 transplanted had a baby). (5) Contrasting with the Andersen et al paper, the fertilization rate reported by Hjorth et al was very low (38%). The low live birth rate (18%) was also much lower than the rate reported by the same team in 2015 (31%). The paper by Hjorth et al (4), reports in breast cancer patients (n=14) only 1 patient that delivered a baby (1/14= 7%). Among the 14 other patients, 4 patients delivered at least 1 baby (4/14 = 29%). In total, only 5 out of 28 patients had a baby.

In summary, this paper is interesting, but it does not seem to be representative of the current literature on ovarian tissue freezing. The population presented in this manuscript consists of patients undergoing IVF on frozen-thawed-grafted tissue, and this situation is known to bear poorer results than IVF on native ovaries in the general population. Colleagues working in fertility preservation should continue to offer ovarian tissue freezing and oocyte or embryo freezing are also viable options in many cases.

References

1) Practice Committee of the American Society for Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion (2019). Fertil Steril 2019;112:1022-1033.
2) Donnez J and Dolmans MM. Fertility preservation in women. NEJM 2017 (377): 1657-1664.
3) Shapira M, Dolmans MM, Silber S, Meirow D. Evaluation of ovarian tissue transplantation - results from three clinical centers. Fertil Steril. 2020 (in press).
4) Hjorth IMD, Kristensen SG, Dueholm M, Humaidan P. Reproductive outcomes after IVF treatment in a cohort of Danish women transplanted with cryopreserved ovarian tissue. Fertil Steril, 2020, present issue.
5) Andersen ST, Pors SE, Poulsen LC, Colmorn LB, Macklon KT, Ernst E, Humaidan P, Andersen CY, Kristensen SG Ovarian stimulation and assisted reproductive technology outcomes in women transplanted with cryopreserved ovarian tissue: a systematic review. Fertil Steril. 2019 Nov;112(5):908-921

Highlighted Revision

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Editorial on
Fertil Steril 29512
"Reproductive outcomes after IVF treatment in a cohort of Danish women transplanted with cryopreserved ovarian tissue"

Title: ~~Reaching unreachable conclusions: th~~The importance of patient selection to analyze IVF outcome with transplanted cryopreserved ovarian tissue

Dolmans MM[a,b], Falcone T[c], Patrizio P[d]

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~~ISFP~~

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Meeting the increasing demand for fertility preservation remains a challenge. Indeed, with increasing success of oncological treatments, offering ~~proposal of~~ fertility preservation before gonadotoxic treatment should be the standard of care ~~becomes a moral obligation.~~ Hematologic and breast cancers represent the most frequent indications for fertility preservation, especially because they are cancers with the highest prevalence in ~~the~~ the reproductive age group. Besides embryo cryopreservation and oocyte vitrification, ovarian tissue cryopreservation (OTT) is often proposed as fertility preservation option in specific indications such as prepubertal girls and women who cannot delay the onset of chemotherapy for ovarian stimulation.

The excellent outcomes of fertility preservation in general and ovarian tissue cryopreservation in particular have convinced oncologists to refer their patients to reproductive medicine specialists. Since its first implementation for cancer patients in 1996, followed by the first live birth in a Hodgkin's lymphoma patient in 2004, ovarian tissue cryopreservation is now accepted by ASRM as a fertility preservation option that is not experimental (1).

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Ovarian tissue auto-transplantation has been performed worldwide, and after reimplantation of the frozen-thawed tissue into the pelvic cavity, ovarian activity is restored in over 95% of cases (2). Pregnancies and live births with that technique have started to climb steadily, showing an exponential increase, with the number of live births as of June 2017 exceeding 130 (2) and probably more than 200 in 2020.

Analyzing the percentage of transplanted patients in terms of success rate, 3 major centers (Sheba Medical center in Tel Aviv, Cliniques universitaires Saint Luc in Brussels and Infertility center in St Louis) report in 2020 in a series of 60 patients, a pregnancy rate of 50% and a live birth rate of 41% (3). These results prove the efficacy of the technique and support its use when fertility preservation is needed.

However, the success rates of OTT are not always reproducible, even within the same IVF units. The manuscript in this issue of F&S is ~~another~~ proof of how important it is to carefully collect and analyze clinical data. (4) ~~before risking of reaching unreachable conclusions. Poor and s~~Skewed patient selection and , incomplete ~~and confusing~~ data collection, may ~~unexplainable omissions of established recommendations,~~ leave the readers with ~~unnecessary~~ doubts on the efficacy of OTT. Indeed, ~~O~~one clear take home message from this work is the confirmation that ovarian tissue freezing is a robust option for some patients needing fertility preservation. In fact, the frozen tissue was cryopreserved (even if transported for up to 6 hours on ice), thawed and re-grafted successfully in all cases. However,~~But~~ what needs more caution is the interpretation of the ~~then the~~ IVF data for~~on~~ this cohort of Danish women ~~become uninterpretable~~.

First, the small number of patients advised to undergo IVF after OTT were ~~poorly selected and~~ highly heterogeneous. Indeed, two (cases 19 and 28) had whole body radiation requiring peritoneal ~~ovarian tissue transplant (~~OTT~~)~~ assuming ovarian atrophy, but there was no mention of possible impact on the uterus. In addition, ~~there were~~ some patients ~~that~~ had already undergone IVF prior to the OTT, but these data were not presented, and 5 patients had elevated FSH levels already at the time of the first ovarian stimulation (therefore they were already very poor prognosis).

Furthermore, ~~It is also confusing the statement of~~ 9 patients ~~that~~ had no ovarian response at their first IVF and ~~of these~~ 4 underwent a second OTT before even doing the first IVF cycle. ~~(how can this be?!)~~ Finally, 2 of the patients that had the second OTT dropped out from additional IVF cycles and one wonders if they resumed their ovarian function and perhaps had a spontaneous pregnancy (assuming they were in the group of orthotopic ovarian grafting).

~~Very confusing is trying to understand the rationale of doing OTT on both ovaries and peritoneal sites (cases 1, 8, 13, 14, 17 and 26). Or why to perform a peritoneal transplant for cases 25 and 28 that were not menopausal when they had their first OTT?~~

Second, the authors provided no information on the steroid receptor status for 12/14 patients with breast cancer and similarly they had no information about follicular density on the histological samples prior to cryopreservation. This information may provide helpful in anticipating ovarian response and thus IVF outcome.

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Third, it is unclear ~~one can wonder~~ why oocyte freezing was not offered to the breast cancer patients. Indeed, oocyte freezing is recommended in these patients by American Society of Clinical Oncology (ASCO)~~ASCO~~ guidelines of 2006, and later by ASRM, ESHRE and International Society for Fertility Preservation (ISFP). ~~Third, there is no valid explanation on why oocyte freezing was not offered. The authors claimed that the patients in their cohort had their ovarian tissue cryopreserved from the year 2008 onwards, however at the time oocyte freezing was already a viable option as recommended by ASCO guidelines of 2006 and later by ASRM, ESHRE and ISFP~~.

Fourth,~~Third~~~~Fourth,~~ it becomes difficult ~~is puzzling to try~~ to reconcile these poor IVF results of this study ~~(poor)~~ with the data ~~(good)~~ that the same group has published extensively on this same topic in previous reports. Nonetheless, it is important to know that for certain selected patients as described here, OTT and subsequent IVF data cannot be extrapolated to the success rates known in literature. The high rate of pregnancy losses, some even in the second trimester, if confirmed from additional studies, requires proper patient counseling.

~~Fifth, no explanation for the very high pregnancy loss rate, including no explanation for losses in the second trimester.~~

~~Sixth, the IVF was performed in 5 different clinics and laboratory thus it is possible that success rates might have been impacted.~~

An interesting observation that certainly deserves more studies is the 36% empty follicle rate. This specific question has been previously reported. For example in a report from Belgium, the empty follicle rate was 29 %, and the fertilization rate of 50% ~~*(Dolmans et al, Human Reprod 2009(24) : 2778–2787)*~~. ~~It should be focused that t~~These patients were those that had~~ve~~ not achieved spontaneous pregnancy after 1 year of menstrual cycling.
The possible causes of empty follicle syndrome were previously ~~r~~ reported ~~in a previous editorial on the same topic (5)~~ and include i) dysfunctional folliculogenesis due to elevated basal FSH concentrations during the early follicular phase, ii) asynchrony between granulosa cell maturation and oocyte maturation, and iii) damage to the oocyte itself by freezing, thawing and transplantation, leading to a higher rate of empty follicles or oocyte alterations, while granulosa cells may be more resistant.

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In summary, this paper is interesting, but it does not seem to be ~~not~~ representative of the current literature on ovarian tissue freezing ~~and certainly not representative of data of their own center~~. The population presented in this manuscript consists of patients undergoing IVF on frozen-thawed-grafted tissue, and this situation is known to bear poorer results than IVF on native

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ovaries in the general population ~~(5)~~. Colleagues working in fertility preservation should continue to offer ovarian tissue freezing and oocyte or embryo freezing are also viable options in many cases.

References

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