

GYNECOLOGY

Modeling delay of age at natural menopause with planned tissue cryopreservation and autologous transplantation



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BACKGROUND: Ovarian tissue cryopreservation has been proven to preserve fertility against gonadotoxic treatments. It has not been clear how this procedure would perform if planned for slowing ovarian aging.

OBJECTIVE: This study aimed to determine the feasibility of cryopreserving ovarian tissue to extend reproductive life span and delay menopause by autotransplantation near menopause.

STUDY DESIGN: Based on the existing biological data on follicle loss rates, a stochastic model of primordial follicle wastage was developed to determine the years of delay in menopause (denoted by D) by ovarian tissue cryopreservation and transplantation near menopause. Our model accounted for (1) age at ovarian tissue harvest (21–40 years), (2) the amount of ovarian cortex harvested, (3) transplantation of harvested tissues in single vs multiple procedures (fractionation), and (4) posttransplant follicle survival (40% [conservative] vs 80% [improved] vs 100% [ideal or hypothetical]).

RESULTS: Our model predicted that, for most women aged <40 years, ovarian tissue cryopreservation and transplantation would result in a significant delay in menopause. The advantage is greater if the follicle loss after transplant can be minimized. As an example, the delay in menopause (D) for a woman with a median ovarian reserve who cryopreserves 25% of her ovarian cortex at the age of 25 years and for whom 40% of follicles

survive after transplantation would be approximately 11.8 years, but this extends to 15.5 years if the survival is 80%. As another novel finding, spreading the same amount of tissue to repetitive transplants significantly extends the benefit. For example, for the same 25-year-old woman with a median ovarian reserve, 25% cortex removal, and 40% follicle survival, fractionating the transplants to 3 or 6 procedures would result in the corresponding delay in menopause (D) of 23 or 31 years. The same conditions (3 or 6 procedures) would delay menopause as much as 47 years if posttransplant follicle survival is improved to 80% with modern approaches. An interactive Web tool was created to test all variables and the feasibility of ovarian tissue freezing and transplantation to delay ovarian aging ([here](#)).

CONCLUSION: Our model predicts that with harvesting at earlier adult ages and better transplant techniques, a significant menopause postponement and, potentially, fertile life span extension can be achieved by ovarian tissue cryopreservation and transplantation in healthy women.

Key words: fertility extension, fertility preservation, menopausal symptoms, menopause, menopause delay, ovarian tissue cryopreservation, ovary

Introduction

The human ovarian cortex contains dormant primordial follicles (PFs) that are the reserve from which a limited number of ovulatory follicles bestow the individual fertility potential after puberty. Because developing follicles engage in cyclical hormone production in women, PF exhaustion timing determines the age at natural menopause (ANM).^{1–6} Previous studies of human ovarian tissue provided quantitative information about how PF numbers

decline over time.^{3,7,8} Although there can be >1,000,000 PFs at birth, only approximately 500 ovulate during the reproductive years. Moreover, 99.9% of the ovarian reserve is lost to follicle atresia, and physiological reasons for this apparent “oversupply” have been proposed.⁹ An initial characterization of the spatial distribution of follicles in the human ovary, including resting PFs, has been published recently⁴; this provides a framework for our understanding of spatiotemporal follicle loss over time.

Despite the significant extension of human life in the last 50 years,¹⁰ no proven intervention that delays ANM is available. Women still experience menopause at a mean age of 51.4 years in North America.^{11,12} As reported in the first successful case of ovarian cortex transplantation for a medical indication, the procedure can restore ovarian endocrine function, and the menopausal state can be reversed.^{13,14} The procedure

has evolved in the last 2 decades with increasing success in patients with cancer, resulting in hundreds of live births worldwide.¹⁴ Therefore, in 2019, ovarian cortex cryopreservation and transplantation were removed from the experimental category for medical indications by the American Society for Reproductive Medicine, followed by other professional organizations globally.^{14–18} However, whether planned ovarian cryopreservation can also be used to extend the duration of reproductive function and delay menopause is in question.

Our previous work allows us to address issues surrounding resection, cryopreservation, and return of ovarian cortex; we have established a mathematical model of PF behavior^{19,20} that recapitulates patterns of ovarian follicle loss in individual women and also produces the ANM population distribution when simulations are compiled. The

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AJOG at a Glance

Why was this study conducted?

Ovarian tissue cryopreservation followed by autologous transplantation has been proven to preserve fertility and reverse menopause and is no longer considered experimental for cancer survivors. However, its feasibility in delaying menopause and extending reproductive life in healthy women has not been tested. Using data from previous biological studies that quantified the ovarian reserve at all ages throughout the reproductive life span and determined the growth initiation pattern of primordial follicles that make up the ovarian reserve, we created a mathematical model.

Key findings

The model predicts the likelihood of success based on the age at ovarian tissue freezing, the amount of ovarian reserve frozen and the number of transplants, and posttransplantation survival of ovarian follicles in the tissue. Based on this model, we found that menopause can be markedly delayed for females aged <40 years undergoing ovarian tissue freezing. If ovarian tissue can be frozen under the age of 30 years, in theory, menopause can even be eliminated in some cases. However, the clinical feasibility of delaying menopause beyond the age of 60 years needs to be clinically evaluated.

What does this add to what is known?

Our study shows that planned ovarian tissue freezing and autologous transplantation can extend reproductive life for women aged <40 years. An interactive tool is provided to simulate case scenarios for women at specific ages as determined by model conditions. The interactive tool can be used to determine the feasibility of planned ovarian tissue freezing should this procedure be clinically considered.

model was based on our identification of fluctuating stochastic signals that occur in PFs that affect whether they stay dormant or begin to grow.²¹

After establishing patient-specific boundaries, including the known distribution of PF numbers during postnatal life, the mathematical model was applied to questions surrounding planned ovarian tissue harvest and transplantation. First, is there an optimal chronological age when the ovarian cortex should be removed? Next, how much cortex should be removed from each patient (as a percentage of total ovarian cortex)? Posttransplant ischemia is associated with up to 60% of all follicle losses in the cortex tissue.^{22,23} With this in mind, how does follicle loss after transplant affect ovarian function after tissue return? Last, would outcomes differ if all cryopreserved tissue was returned in single vs multiple procedures? We developed an interactive tool to investigate how these factors would

influence ovarian aging after planned ovarian tissue harvesting and transplantation and address how outcomes could be optimized for (simulated) women. The feasibility and implications of the approach are considered.

Materials and Methods

Efficacy in this study is the induced menopausal delay (denoted D), defined as the difference between the age of menopause with and without tissue harvesting and transplantation. The main mathematical result that we use to study this process is the following formula for menopause delay:

$$D = \frac{1}{\lambda} \ln(1 - p) + \frac{R}{\lambda} \ln \left(1 + \frac{ps}{R} e^{\lambda(T_0 - t_0)} \right) \quad (1)$$

In [formula \(1\)](#), p is the percentage of cortex removed; s is the fraction of removed cortex which survives removal,

cryopreservation, and transplantation; t_0 is the age at tissue removal; T_0 denotes ANM in the absence of planned ovarian tissue harvesting and transplantation; R is the number of surgical returns; and λ is the decay rate of PFs within the ovaries. The Supplementary Information section includes a detailed mathematical derivation of formula (1), and comparisons between this article's and historical models are provided. An interactive tool is available for public use at <https://www.fertilitypreservation.org/contents/probability-calculator/nopause-calculator>.

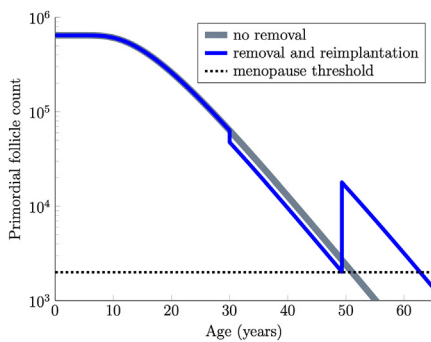
Results**Ovarian tissue harvesting, cryopreservation, and transplantation to delay menopause**

Study parameters were established as follows. *Menopause delay* (denoted D) of planned ovarian tissue harvesting and transplantation is *the increase in menopausal age that results from the intervention*. Mathematically, D can be expressed as:

$$D = (\text{menopause age with intervention}) - (\text{menopause age without intervention}).$$

The concept is shown in [Figure 1](#). The gray curve depicts the declining PF reserve (total number of PFs across both ovaries) in a woman where no intervention takes place. In this example, menopause is reached at the age of 51 years, when the reserve depletes to 2×10^3 remaining PFs (the gray curve crosses the horizontal dashed line). A correspondence between 10^3 remaining PFs per ovary with the timing of the ANM onset was identified in a previous study,³ and we used this menopausal threshold in our original model.¹⁹ The blue curve depicts the same woman if $p=25\%$ of her ovarian cortex (50% of the cortex of 1 ovary) is removed at the age of 30 years, cryopreserved, and returned at the age of 49 years. Ovarian aging was modeled to continue normally from this point, and menopause is shown to be delayed until the age of 62 years (the blue curve crosses the horizontal dashed line). Here, menopause delay D is $62 - 51 = 11$ years.

FIGURE 1
Ovarian harvesting at the age 30 years and peri-menopausal transplantation



The graph shows a comparison between the ovarian aging trajectory of a simulated subject where no intervention has occurred (*gray line*) overlaid with the trajectory of a subject that underwent ovarian cortex removal and cryopreservation at the age 30 years and replacement at age 49 years. Posttransplant ischemic loss of 0% was assumed for this example. The model predicts that the age at natural menopause can be delayed from age 51 years to age 62 years in this simulated recipient.

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Next, we probe how patient and technique variability affects D and assess several key variables: patient age at tissue removal, fraction of total ovarian reserve removed (denoted p), fraction of PFs that survive the procedure (s), and comparison of the performance of transplantation of a cryopreserved cortex at once vs in 3 consecutive fractions. As an example in [Figure 1](#), we simulated interventions using “impending menopause” (when the simulated ovarian reserve reached 2×10^3 remaining PFs) as the time of tissue return to patients to delay menopause. Although we cannot directly measure PF reserve in practice, the intervention can be timed with the change in serum ovarian reserve markers, such as the antimüllerian hormone (AMH) and menstrual changes.²⁴

Impact of age at removal on age at natural menopause delay

[Figure 2](#) summarizes the dependence of menopause delay upon age at tissue removal. First ([Figure 2, A](#)), conditions

were established where $p=25\%$ of the entire ovarian reserve was removed between ages 21 and 40, and $s=100\%$ of PFs survived. Expectedly, earlier tissue removal resulted in greater menopause delay. The dark blue curve shows a delay for a woman born with the population median of 6.4×10^5 PFs.¹⁹ The light blue zone surrounding the dark blue curve shows how delay varies between women according to the distribution of the number of PFs present at birth,³ from women born with the top 10% of PFs (top of the blue zone) down to women born with the bottom 10% (bottom of the blue zone).

Impact of follicle survival after transplant on age at natural menopause delay

Because it is unlikely that $s=100\%$ of PFs will survive after cryopreservation and transplantation, we next investigate how reducing PF survival (fraction s) influences menopause delay. In ovarian xenografting studies, approximately 40% of PFs survive after thawing and transplantation of human tissue.^{22,23} Although the survival rate in patients is not known, ovarian transplant longevity is presumed to be reduced compared with a nontransplanted ovary.¹⁸ However, technological advances, including revascularizing pharmacologic approaches and robotic surgery, may improve follicle survival.^{15,18} Therefore, we include a conservative 40% survival and an improved 80% survival in our models. [Supplemental Figure S1](#) provides probability density curves for 80% survival and tissue removal at ages 25, 30, 35, or 40 years.

Impact of amount of tissue removed and transplanted on age at natural menopause delay

[Figure 2, B](#), shows the optimal tissue removal percentage assuming PF survival of $s=40\%$ (red) or $s=80\%$ (blue). Here, the optimal removal percentage is defined as the one that maximizes menopause delay D . As patient age at removal increases, the optimal amount of ovarian cortex to remove declines, and this again is greatly affected by ovarian reserve size (blue and red shaded areas:

middle 80% of ovarian reserve; dark curves: median ovarian reserve). Although removing approximately 50% of all ovarian cortices maximizes D for women early in the age range, removing less tissue is preferable in later ages. Ovarian reserve size again influences the amount of tissue to remove, where women with larger numbers of PFs experience greater menopause delay when a larger percentage of the cortex is removed. Conversely, women with lower numbers of PFs experience greater D when a smaller amount of cortex is removed.

Impact of primordial follicle survival upon age at natural menopause delay

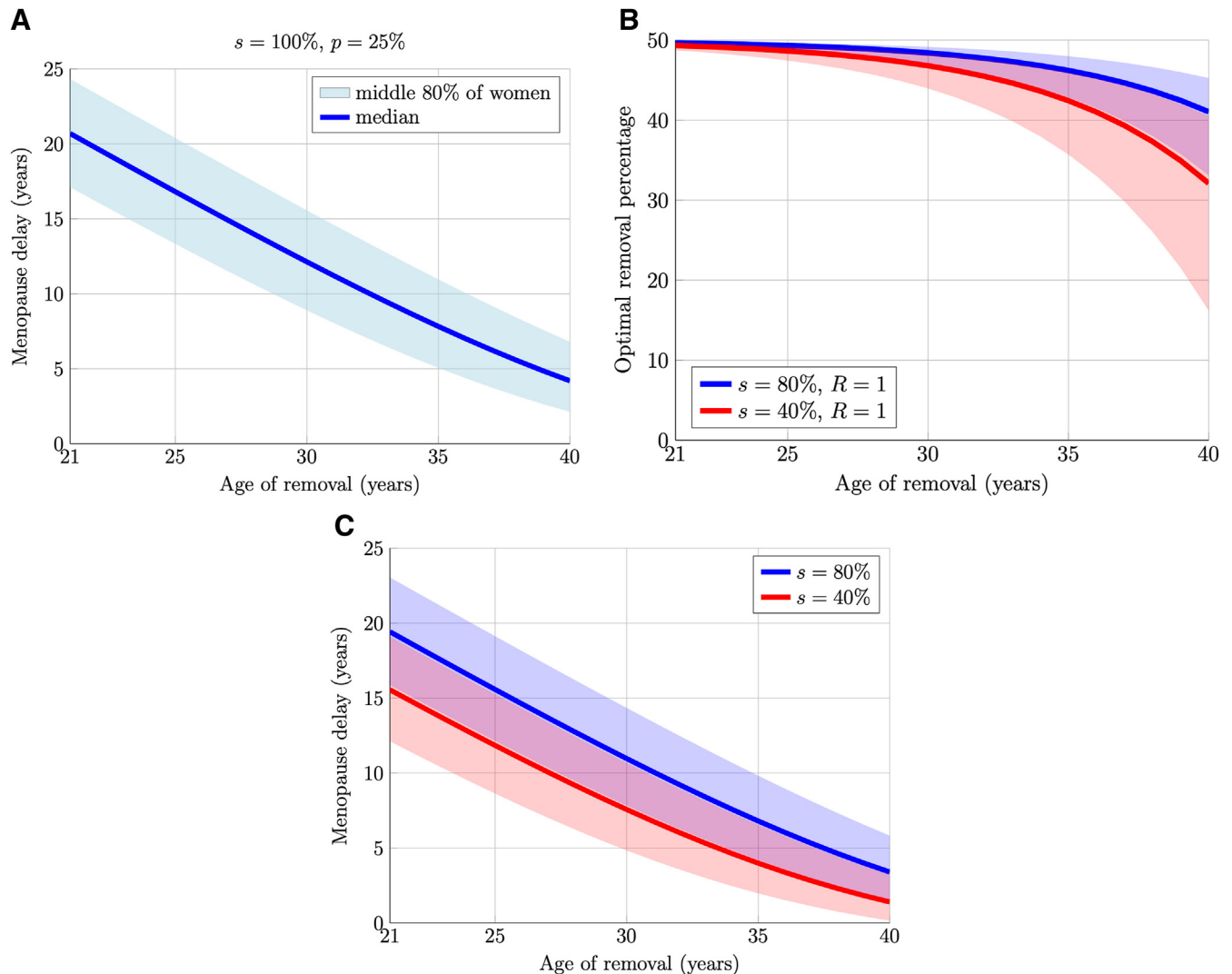
[Figure 2, C](#), shows that, when $s=40\%$ of PFs survive (red zone), removal and return of $p=25\%$ of tissue yield a D of approximately 12 years for a woman with a median ovarian reserve (red line) when tissue is collected at the age of 25 years. D declines through a collection age of 40 years, where ANM is postponed by approximately 1.5 years. Analogous to [Figure 2](#), the “height” of the red zone represents the middle 80% of ovarian reserve and shows that the greater their reserve, the greater their menopause delay. If tissue is removed at the age of 40 years and returned near menopause, a woman at the lowest end of ovarian reserve would experience no delay in ANM. Naturally, doubling PF survival to $s=80\%$ (blue zone, the dark blue line is the median ovarian reserve) increases menopause delay across the time span. Predicted D for a woman born with the median PF number when 25% of her ovarian reserve is removed at ages 25, 30, 35, and 40 years, given differential PF survival s is provided in the [Table](#).

Impact of number of transplants on menopause delay

Finally, we consider how D varies between the return of all cryopreserved cortex at once vs in 3 consecutive transplants (R). [Figure 3](#) and [Supplemental Figure S2](#) compare PF decay between $R=1$ (green zone) and $R=3$ (purple zone). The age range at removal was 21 to 40 years, and the

FIGURE 2

Influence of age, amount of tissue preserved and post-transplant survival on menopause delay



A, The graph shows the expected delay of the age at natural menopause when $p=25\%$ of the whole ovarian cortex is cryopreserved and returned with a PF survival of $s=100\%$. The blue shaded area indicates women born with the middle 80% of PF reserve, and the blue lines indicates the median values. **B,** The graph shows the optimal amount of tissue to remove and cryopreserve as a percentage across the range of patient ages, to maximize the delay of the age of menopause. Older patients benefit from lower amounts of tissue removed, although the overall benefit of ovarian tissue harvesting and transplantation declines with age. **C,** The graph shows menopause delay affected by setting postthaw and transplant PF survival to either 40 or 80%, with similar amount and age at removal as in (A). A single nonfractionated transplant was modeled. Figure 3 shows the benefit of fractionated transplants. PF, primordial follicle.

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tissue was returned near menopause with PF survival $s=40\%$ (Figure 3, A) or 80% (Figure 3, B). Of note, 3 surgical returns of one-third of the removed cortex resulted in a greater menopause delay (more returns always increase the delay, although the marginal increase in

delay decreases as the number of returns grows). Women at the age of 30 years with 3 tissue returns are predicted to experience delayed ANM with a lower limit near 8 years but an upper limit near 20 years. The interactive tool was used to interrogate 6 (and even more) tissue

returns, and given 80% PF survival, the upper limit of ANM delay can exceed 4 decades. In addition, our analysis predicts that returning an equal amount of cortex at each transplant results in a larger menopause delay compared with returning unequal amounts.

Comment

Principal findings

Our analysis predicts that harvesting tissue earlier in life (eg, by the age of 30 years) may allow women to delay menopause significantly, whereas the delay is reduced if harvest occurs near or after the age of 40 years and particularly so for women with a low ovarian reserve at birth. The PF survival rate after cryopreservation and transplant ischemia is a key variable, and our analysis predicts that survival may need to be near 100% for harvest after the age of 40 years to be worthwhile for most women. In addition, our analysis predicts that the fractionation of cryopreserved tissues into multiple transplants maximizes the delay in ANM.

For tissue harvested at the age of 30 years, returning one-third of the removed cortex in 3 separate surgeries delays menopause by at least 12 years for most women, even when only $s=40\%$ of follicles survive after transplantation. The biological rationale for this finding is that when all follicles are reimplanted at once, their loss because of growth activation and oocyte aging occurs concurrently. However, when fractionated, ovarian aging within still-frozen tissue remains suspended until transplantation.

Finally, our analysis predicts how the effects of planned ovarian tissue harvesting and transplantation vary across a population of women. Such variability is to be expected, considering the variability in PF endowment at birth³ that corresponds to ANM variability.²⁵ Women with large PF reserves may benefit greatly, but planned ovarian tissue harvesting and transplantation may not be advisable for women with small PF reserves. Although seemingly paradoxical, our model predicts that women with lower ovarian reserve should preserve smaller amounts of ovarian tissue. This is because the removal of a large portion of the cortex may immediately exhaust the ovarian reserve. Planning should be informed by the model provided here and also ovarian reserve assessment, such as by serum

TABLE

Menopause delay given cryopreservation of 25% of ovarian reserve (50% of an ovarian cortex) at indicated ages and percentage primordial follicle survival

25% reserve removal:	Patient Age at Tissue Harvesting			
	25	30	35	40
Follicle reserve survival post-transplantation (%)	Menopause delay (D, years)*			
40%	11.8	7.6	4.0	1.4
80%	15.6	11.0	6.8	3.4
100%	16.8	12.1	7.8	4.2

* Anticipated delay in menopause for median woman.
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measurements of AMH. Reserve assessment can place candidates into 3 categories—expected, below expected, and above expected—allowing outcomes to be modeled. This may lead to the decision to forgo the treatment in some cases, whereas the procedure may be justified even in more advanced ages in other cases.

Results in the context of what is known

No treatment is available to delay menopause and extend the natural fertility period in women, and ovarian tissue freezing may be the first successful approach. Our modeling of biological PF behavior provides a starting point for testing ovarian tissue cryopreservation and transplantation to delay menopause in healthy women.

Clinical implications

Combined with the recent success of ovarian tissue cryopreservation in patients who preserved their tissues before chemotherapy, our work suggests that performing the procedure in healthy women would likely extend ovarian function and, potentially, the fertile life span. The provided model allows optimization of the amount and the timing of tissue harvest for cryopreservation and the transplantation strategy.

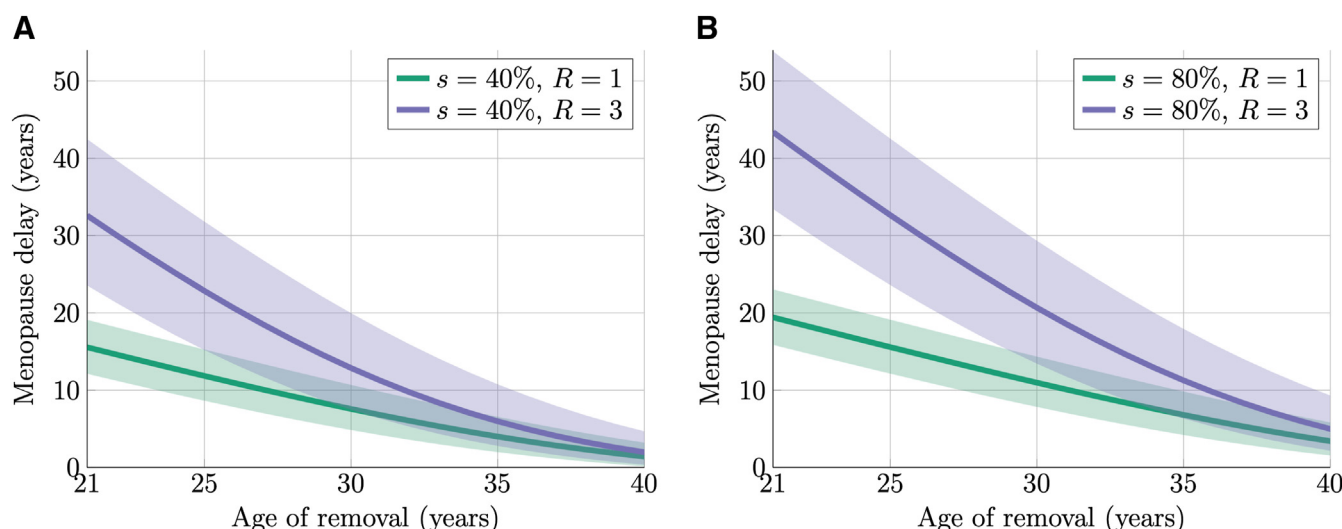
Some health concerns have been cited with extended natural estrogen production. One of the commonly cited risks is breast cancer, as the incidence is

generally higher in women with late menopause.^{26,27} However, not only is this risk small but also is based on a reanalysis of the Women’s Health Initiative data; the benefits of continued estrogenization (here, synthetic hormones) outweigh the clinical risks.²⁸ Natural menopause has been recorded as late as at the age of 62 years.²⁹ One can infer that delaying menopause to around the age of 60 years should not be considered “unnatural,” and potentially, significant benefits, including improved quality of life, can result within this time frame. These can include reduced risk of cardiovascular disease, stroke, atherosclerosis, and osteoporosis.³⁰ Presented with an accurate risk assessment that includes family history and individual genetic information, women can consider the age at ovarian tissue transplantation that is appropriate for them.

For most women, menopause will occur >10 to 15 years after cryopreservation. During this time, new information is likely to emerge that can further optimize transplantation timing. The amount of ovarian tissue transplanted can be based on patient risk perception and available risk-benefit information, to achieve an appropriate and safe delay in menopausal age. If extending menopause beyond 60 years of age is supported as safe, patients can return for repeated transplantations. Additional surgical procedures can be avoided by harvesting ovarian tissue during medically indicated procedures, such as

FIGURE 3

Effect of fractionated ovarian tissue transplantation on the delay of ANM



The expected delay in menopausal onset is compared under the following conditions. Of note, 25% of all cortices are harvested between the ages of 21 and 40 years, and primordial follicle survival s is 40% (A) or 80% (B). Tissue transplantation is modeled as occurring either once or 3 separate times. The *green shaded area* and *green line* represent the outcomes for 1 surgical return for the middle 80% of simulated subjects and the median simulated subject, respectively. The *purple shaded area* and *line* are those same outcomes for 3 cortex return procedures. The figures show that, by fractionated transplantation, the menopause delay can be further extended. As an example, if the tissue was harvested at the age of 25 years with 40% follicle survival, 15 to 31 years of delay in ANM would be expected by transplanting 3 fractions compared with 8 to 15 years if all tissues were transplanted at once (A). If posttransplant follicle survival was 80% and 3 transplantations occurred (B, *purple*) using tissue harvested at the age of 25 years, the predicted delay can be 24 to 42 years, theoretically eliminating menopause during the average female life span.

ANM, age at natural menopause.

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cesarean deliveries, tubal ligations, endometriosis surgeries, and others.^{14,17}

As simple techniques of subcutaneous ovarian tissue transplantation have been developed by the senior author of this report,^{31,32} transplants can be performed under local anesthesia in the office setting, with minimal discomfort and cost.

Research implications

Although we can derive confidence intervals for the duration of ovarian aging so that the “best” and “worst” case scenarios can be considered (see the Strengths and limitations section), it is crucial that we compare patient outcomes given varied timing, amount of tissue removed, etc. with model output. For now, we can provide first-of-their-kind expected outcomes, and the model can only be entirely validated moving forward. We anticipate that, given the relatively consistent performance of

ovarian tissue transplants in patients with cancer, the procedure should yield similar or better results, particularly because this healthy population is not confounded by malignancies or their treatments.

A crucial near-term research objective is ensuring that the greatest number of PFs survive after transplantation, to maximize expected ANM delay and health benefits. Progress has been made in that area with approaches that greatly enhance posttransplantation follicle survival. These include neovascularizing agents,¹⁴ such as sphingosine-1-phosphate,³³ perioperative pharmacologic treatments, and robotic surgery.^{15,18}

Strengths and limitations

The main strength of our approach is that we can consider the distribution of likely trajectories for ovarian aging after tissue removal and transplantation and estimate patient variability. Because we

account for acute PF loss after transplantation and simulate ovarian aging outcomes given differential acute loss, our model provides realistic predictions of the “best” and “worst” case scenarios. Because of variables that, for now, cannot be accounted for (study limitations indicated below), determining ranges of possible outcomes is crucial.

A limitation of this approach is its dependence on a somewhat uniform spatial distribution of PFs within harvested tissue. Our focus on relatively young ages for the removal of tissue means that we expect a high density of PFs per unit volume of tissue.^{34,35} Follicle distribution may be more variable in older patient specimens, and this could lead to variable performance after transplantation. This will be difficult to address until rapid, indirect estimation of viable follicle numbers within the tissue can be achieved. Given the removal of at least 25% of the reserve is

usually indicated for efficacious menopause delay, differences in follicle density within different volumes of ovarian cortex should balance out.

Conclusions

Our mathematical model, derived from biological data of human PF decay over time, indicates that ovarian tissue cryopreservation and transplantation can significantly delay the ANM in women aged <40 years. Output suggests that, even under circumstances where post-transplant follicle loss is at its worst, menopause could be delayed by many years given “early” tissue removal and perimenopausal replacement. Delay can be further extended by a fractionated return.

As transplantation and revascularization enhancement methods continue to improve posttransplantation follicle survival, this strategy may become more feasible for older women, with less tissue needed for younger individuals.¹⁴ Although model validation will require a series of cases to be monitored over lengthy periods, intervention efficacy after transplant will be detectable earlier than the ages of expected menopause. For example, ongoing menstrual cyclicity and premenopausal AMH levels will indicate that ovarian function has been extended.³⁶ Here, the tool provided will allow clinicians, translational scientists, and patients to gauge the feasibility of planned ovarian tissue freezing to delay menopause. ■

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