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Research Article

Why is there an "oversupply" of human ovarian follicles?†

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Abstract

Women are born with hundreds of thousands to over a million primordial ovarian follicles (PFs) in their ovarian reserve. However, only a few hundred PFs will ever ovulate and produce a mature egg. Why are hundreds of thousands of PFs endowed around the time of birth when far fewer follicles are required for ongoing ovarian endocrine function and only a few hundred will survive to ovulate? Recent experimental, bioinformatics, and mathematical analyses support the hypothesis that PF growth activation (PFGA) is inherently stochastic. In this paper, we propose that the oversupply of PFs at birth enables a simple stochastic PFGA mechanism to yield a steady supply of growing follicles that lasts for several decades. Assuming stochastic PFGA, we apply extreme value theory to histological PF count data to show that the supply of growing follicles is remarkably robust to a variety of perturbations and that the timing of ovarian function cessation (age of natural menopause) is surprisingly tightly controlled. Though stochasticity is often viewed as an obstacle in physiology and PF oversupply has been called "wasteful," this analysis suggests that stochastic PFGA and PF oversupply function together to ensure robust and reliable female reproductive aging.

Summary Sentence
Mathematical extreme value theory analysis of human primordial follicle numbers over time supports the hypothesis that the large endowment of primordial follicles at birth enables a simple stochastic PFGA mechanism to yield a steady supply of growing follicles that lasts for several decades.

Keywords: extreme value theory, female reproductive aging, menopause, ovary, primordial follicles

Introduction

Women are born with an ovarian reserve of around $N = 10^5$ to $N = 10^6$ primordial ovarian follicles (PFs). This reserve then decreases over the next several decades as individual PFs begin to grow and progress through several stages of development. Only a small fraction of follicles ever reach the ovulatory stage, as the vast majority of follicles ($\approx 99.9\%$) die prior to ovulation. Menopause, which marks the end of menstrual cyclicity, occurs when the ovarian reserve dips below a threshold of around $k = 10^3$ PFs [1].

Cross-sectional data on how the number of PFs in the ovarian reserve decays with age have been obtained in many histological studies dating back to the 1950s [1–8]. Based on these data, several groups have proposed mathematical formulas to quantify PF decay with age [7, 9–14]. Though the specific mathematical formulas vary, most of these prior analyses have found that the logarithm of the PF count decays linearly or almost linearly with age in the decade or two prior to menopause. This means that the PF count decays roughly exponentially at sufficiently large age.

A major goal in reproductive biology and medicine is to determine what dictates the decision of individual PFs to awaken from dormancy via growth activation or atresia. This is because a better understanding of mechanisms that control the behavior of individual PFs should lead to a clearer understanding of the control of ovarian aging overall, and potentially, to interventions that might prevent the early loss of ovarian function. The notion that such PF growth activation (PFGA) may be stochastic has a long history. Faddy and Gosden [10] introduced a stochastic model of PFGA in women, in which each of the N PFs present at birth leaves the ovarian reserve at independent and identically distributed random times. More precisely, if $\tau_1, \tau_2, \dots, \tau_N$ denote the PFGA times of the N PFs (i.e. the times that each PF leaves the reserve through growth activation or, rarely, atresia), then Faddy and Gosden [10] assumed that

$$\tau_1, \tau_2, \dots, \tau_N \text{ are independent and identically distributed,} \tag{1}$$

with a probability distribution that decays exponentially for sufficiently large age t,

$$\mathbf{P}(\tau > t) = Ae^{-\lambda t}, \quad \text{if } t \geq t_0. \tag{2}$$

In Faddy and Gosden [10], the parameters in formula (2) were $\lambda = 0.3$/year, $A = e^{9.3}$, and $t_0 = 38$ years. This human stochastic PFGA model in Faddy and Gosden [10] was very similar to earlier stochastic mouse PFGA models proposed by Faddy, Jones, and Edwards [15] and Faddy, Gosden, and Edwards [16]. Assuming equations (1) and (2) implies that the expected number of PFs in the reserve at age t, denoted $F(t)$, decays exponentially according to

$$F(t) = NAe^{-\lambda t}, \quad \text{if } t \geq t_0. \tag{3}$$

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In a similar human PFGA model, Faddy et al. [9] fit PF count data [1–4] to a function $F(t)$ satisfying formula (3) with $\lambda = 0.24$/year, $N = 9.5 \times 10^5$, $A = e^{5.3}$, and $t_0 = 37.5$ years. In a review of folliculogenesis in mammals, Hirshfield discussed PFGA as possibly a "randomized stochastic event, similar to radioactive decay" [17]. Finch and Kirkwood [18] discussed "pure chance" PFGA and described the similarity of the decay of PFs in the reserve to radioactive decay. Of course, radioactive decay follows formulas (1)–(3).

The satisfying outcomes achieved when ovarian aging was modeled as a stochastic process have recently been supported by experimental, bioinformatics, and mathematical results [14, 19, 20]. This new work supports the hypothesis that PFGA is controlled by a biological stochastic process, cellular response to damage by the integrated stress response (ISR) pathway [21, 22]. Specifically, the hypothesis sets out that ISR checkpoint resolution after physiological stress and DNA damage in individual PFs allows entrance into the cell cycle, and thus PFGA. If PF response to ISR-activating stressors is modeled by a stochastic process, this results in a stochastic PFGA time for each PF. This stochastic model was found to recapitulate the patterns observed in nature for both (i) PF decay over time within individual women and (ii) the timing of PF depletion in populations of women equivalent to the distribution of the human age of natural menopause (ANM) [14]. In aggregate, the "wet laboratory" work combined with stochastic modeling leads to a plausible overall model of PF behavior during ovarian aging.

A striking feature of the ovarian system is its apparent redundancy or "wastefulness" [10, 23–27]. As mentioned above, out of a "starting supply" with an upper limit around $N = 10^6$ PFs at birth, approximately 99.9% are destined to die [9, 11]. Only about one follicle survives to ovulate per month, and thus over 40 years of menstrual cycles, only about $40 \times 12 \approx 500$ PFs are relevant to possible reproduction across the entire life span. Even counting the follicles that engage in ovarian endocrine function and the signaling required for menstrual cycles, why have hundreds of thousands of PFs when only much smaller numbers are needed? What explains this oversupply of three orders of magnitude? This seeming wastefulness is compounded by the fact that a girl has several million PFs in her reserve a few months before she is born [12].

In this paper, we study the consequences of PF oversupply combined with stochastic PFGA. We find that this combination yields (i) a supply of growing follicles that is remarkably robust to a variety of perturbations and (ii) a tightly controlled ANM (PF depletion time). In particular, the apparently wasteful oversupply of PFs actually serves an important physiological purpose.

Summarizing our results, we first show that prior analysis of PF count data implies that the average PFGA time, $\mathrm{E}[\tau]$, is 20 years or less with a standard deviation of less than 10 years. Hence, PF oversupply extends the female reproductive lifespan by delaying PF depletion far beyond the typical lifespan of a PF. In particular, we use extreme value theory to show that the ANM, denoted T, depends logarithmically on the starting supply N and that N between 10^5 and 10^6 is required to extend T to the range observed in populations of women. Furthermore, we explore the curious empirical fact that though starting supplies N vary significantly across populations of women (N can vary by 1000% between women), the ANM T has a much tighter distribution across populations of women (T varies by at most 50% between healthy women). We show that this disparity between population variability in N versus T is explained simply by the result that T depends logarithmically on N. Hence, stochastic PFGA means that the physiological process of PF formation which establishes N need not be tightly regulated to yield a narrow ANM population distribution [28]. In addition, we address the variability in ANM which stems from stochastic PFGA. If the PFGA time of each PF is stochastic, then one might expect the resulting ANM T to be quite variable. However, we use extreme value theory to show that due to (i) the PF oversupply and (ii) the menopause threshold of roughly $k = 10^3$ PFs remaining in the reserve, the variability in T stemming from stochastic PFGA is only a couple of months. We further show that despite the stochasticity in PFGA, the resulting stream of growing follicles is nearly deterministic. Taken together, our results suggest that PF oversupply and stochastic PFGA function together to ensure robust and reliable patterns of ovarian aging in individual women.

Methods

In this section, we apply extreme value theory to PF behavior and discuss parameter estimation of PF decay.

Extreme value theory

Extreme value theory is a branch of mathematical statistics dealing with extreme events in the tails of probability distributions [29]. Extreme value theory is relevant because the ANM is determined by the slowest ~0.3% of PFs to leave the reserve. That is, extremely "slow" PFs trigger menopause, and extreme value theory studies such statistical outliers.

For a given woman, let N denote the number of PFs in her ovarian reserve at birth, which we call her starting supply. Suppose we label these PFs from 1 to N and let τ_n denote the woman's age when the PF labeled by $n \in \{1, \ldots, N\}$ leaves the reserve (either though growth activation or atresia). We call $\tau_1, \tau_2, \ldots, \tau_N$ the PFGA times.

Following references [10, 14–16], we assume the PFGA times (i) are independent and identically distributed (as in formula (1)) and (ii) have exponentially decaying probability distribution at sufficiently large age (as in formula (2)). Before estimating the decay rate λ and prefactor A in formula (2), we review results from extreme value theory [29].

Menopause occurs when the number of PFs in the reserve drops to around $k = 10^3$ [10, 11, 18, 30]. To express the age of menopause in terms of the PFGA times, $\{\tau_n\}_{n=1}^N$, let

$$T_{1,N} \le T_{2,N} \le \cdots \le T_{N-1,N} \le T_{N,N}$$

denote the order statistics corresponding to $\{\tau_n\}_{n=1}^N$. That is, $T_{j,N}$ denotes the time that the jth PF leaves the reserve,

$$T_{j,N} := \min\left\{\{\tau_1, \ldots, \tau_N\} \setminus \cup_{i=1}^{j-1}\{T_{i,N}\}\right\}, \quad j \in \{1, \ldots, N\}.$$

In this notation, the ANM (i.e. PF depletion time) is

$$T := T_{N-k,N}, \quad \text{where } k = 10^3.$$

Since k is much less than the starting supply N, we can use extreme value theory to estimate the statistics and distribution

of the menopause age T [31]. In particular, Theorem 2 in Lawley and Johnson [31] implies that the expected ANM is well approximated by

$$\mathrm{E}[T] \approx \frac{1}{\lambda}\Big(\ln N + \ln A + \gamma - H_k\Big), \tag{4}$$

where $\gamma \approx 0.58$ is the Euler-Mascheroni constant, and $H_k = \sum_{r=1}^{k} r^{-1}$ is the k-th harmonic number (we note that $H_k \approx 7.5$ for $k = 10^3$). Furthermore, Theorem 2 in Lawley and Johnson [31] implies that the standard deviation of the ANM (denoted $\mathrm{SD}(T)$) is well approximated by

$$\mathrm{SD}(T) \approx \frac{1}{\lambda}\sqrt{\psi'(k+1)}, \tag{5}$$

where $\psi'(k+1) = \sum_{r=0}^{\infty}(r+k+1)^{-2}$ is the first-order polygamma function (we have $\sqrt{\psi'(k+1)} \approx 0.03$ for $k = 10^3$). We note that the mean and variance in formulas (4)–(5) are for a single woman with given parameters N, λ, A, and k. We further note that higher order approximations to the statistics and distribution of T are given in Theorems 1 and 4 in Lawley and Johnson [31].

Parameter estimation

The parameters in the exponential decay in formula (2) can be estimated from histological PF count data, though the precise values of these parameters are not critical to our results.

In Figure 1, we plot the PF count data (black squares) from Wallace and Kelsey [12] (data originally obtained in references [1–8]). The dashed pink line in this plot is the line that best fits the data for ages $t_0 = 25$ years and older (i.e. the line that minimizes square error). For this age range, this linear function fits the data nearly as well as the PF decay curve proposed in Wallace and Kelsey [12] (the sum of squared errors is 1.6% greater for the linear function). Noting the logarithmic scale of the vertical axis, the dashed pink line is the exponentially decaying function in formula (3) where

$$N = 3.2 \times 10^5 \tag{6}$$

is the median of the starting supply data from Wallace and Kelsey [12] and the fitted parameters are

$$\lambda = 0.173/\text{year}, \quad A = e^3. \tag{7}$$

The exact values in formula (7) would change if we change t_0, but for t_0 between 25 years and 40 years, λ ranges between $\lambda = 0.16$/year (with $A = e^{2.4}$) and $\lambda = 0.25$/year (with $A = e^{6.3}$). The estimates of $\lambda = 0.3$/year (with $A = e^{9.3}$ and $t_0 = 38$ years) in Faddy and Gosden [10] and $\lambda = 0.24$/year (with $A = e^{5.3}$and $t_0 = 37.5$ years) in Faddy et al. [9] are similar.

The decay rate λ and the prefactor A in formula (2) can also be estimated from the random walk model in Johnson et al. [14]. The solid curves in Figure 1 show the expected PF decay curves for this random walk model for women with starting supplies $N = 10^5$ (orange curve), $N = 3.2 \times 10^5$ in formula (6) (green curve), and $N = 10^6$ (purple curve). The distribution $\mathbf{P}(\tau > t)$ for this random walk model approximately satisfies

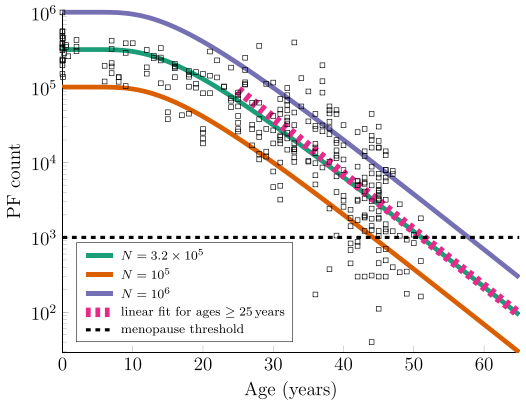

Figure 1. Decay of the number of PFs in the reserve over time. The black square markers are data reported in Wallace and Kelsey [12]. The dashed pink link is the best linear fit to the data after age 25. The horizontal dashed line is the menopause threshold $k = 10^3$. The solid curves are for the random walk model in Johnson et al. [14] with starting supplies $N = 3.2 \times 10^5$ (median), $N = 10^5$ (bottom 1%), and $N = 10^6$ (top 1%).

formula (2) with decay rate and prefactor given by

$$\lambda = 0.172/\text{year}, \quad A = e^{3.1}. \tag{8}$$

For concreteness, we take the values of λ and A in formula (8) in our analysis below. Perturbing the values of λ and A in the ranges mentioned above would have little effect on our results.

Results

Oversupply ensures several decades of fertility

We claim that prior analysis of PF decay data implies that PFs spend only about 20 years or less in the reserve on average. To see this, let $F(t)$ denote the number of PFs remaining in the ovarian reserve at age $t \geq 0$. For such a PF decay curve $F(t)$, we can obtain a survival probability or survival fraction via

$$S(t) := F(t)/F(0), \tag{9}$$

which is the fraction of the starting supply (initial PFs) remaining in the reserve at age $t \geq 0$. Having obtained such a survival probability, we can compute statistics of PFGA times τ, such as the mth moment,

$$\mathrm{E}[\tau^m] = \int_0^\infty m t^{m-1} S(t)\,\mathrm{d}t \tag{10}$$

and the median,

$$\mathrm{median}(\tau) = S^{-1}(1/2),$$

where S^{-1} denotes the inverse of S. The relation (10) is proved in the Supplementary Material.

In Table 1, we give the mean, median, and standard deviation of the PFGA times implied by the PF decay curves $F(t)$ posited by (a) Faddy et al. in 1992 [9], (b) Faddy and Gosden in 1996 [11], (c) Hansen et al. in 2008 [7], (d) Wallace and Kelsey in 2010 [12], and (e) Johnson et al. in 2022 [14]. In Figure 2, we plot these five PF decay curves $F(t)$ given in

Table 1. Mean, median, and standard deviation (in years) of PFGA times τ for the PF decay models proposed in literature [7, 9, 11, 12, 14] using the implied survival probabilities in formula (9).

PF decay curve	Mean	Median	St. dev.
Faddy et al. [9]	10.1	7.1	9.6
Faddy and Gosden [11]	13.3	11.2	11.0
Hansen et al. [7]	20.8	20.2	9.0
Wallace and Kelsey [12]	17.0	16.0	10.3
Johnson et al. [14]	19.6	18.2	7.8

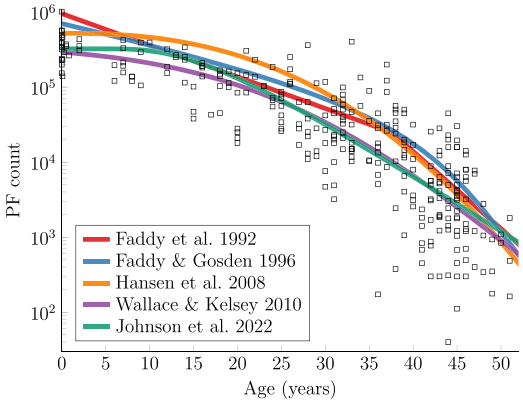

Figure 2. PF decay curves posited in literature [7, 9, 11, 12, 14] and the PF count data reported in Wallace and Kelsey [12].

references [7, 9, 12, 14] (these PF decay curves are reviewed in the Supplementary Material). Though the numerical values in Table 1 vary between the five models, the mean and median of τ are around 20 years or less with a standard deviation of around 10 years (additional statistics of τ are given in Supplemental Table S1).

Since a PF spends only about 20 years in the reserve on average, the vast oversupply can be understood as functioning to extend the female reproductive lifespan by delaying PF depletion far beyond the typical lifespan of a PF. Put another way, the PF oversupply ensures that there are enough outliers which last much longer in the reserve than average. Indeed, to reach the population median ANM of 51 years, a woman needs $k = 1000$ PFs to stay in the reserve 3 standard deviations longer than their mean.

To understand how the ANM T depends on the starting supply N of PFs at birth, we plot the expected ANM as a function of N in Figure 3. The solid black curve is the following extreme value theory estimate of the ANM (see formula (4)),

$$\mathrm{E}[T] \approx \frac{1}{\lambda}\Big(\ln N + \ln A + \gamma - H_k\Big), \tag{11}$$

where $\gamma \approx 0.58$ is the Euler-Mascheroni constant, and $H_k = \sum_{r=1}^{k} r^{-1}$ is the k-th harmonic number (we note that $H_k \approx 7.5$ for $k = 10^3$). The slow logarithmic dependence on N in formula (11) shows that the very large value of the starting supply N is necessary to ensure that the PF supply lasts several decades longer than the typical time a single PF lasts. The red circle markers in Figure 3 are results of stochastic simulations of the random walk model in Johnson et al. [14] for different values of the starting supply N (10^8 stochastic realizations of

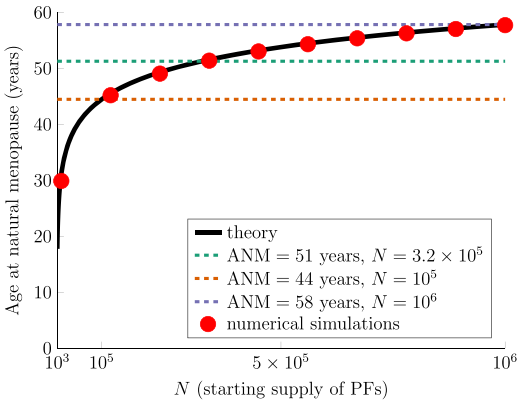

Figure 3. ANM depends logarithmically on the PF starting supply N. The black curve is the extreme value theory estimate in formula (11), which agrees with numerical simulations (red circles) of the random walk model in [14]. The dashed lines show the ANM for starting supplies $N = 3.2 \times 10^5$ (median), $N = 10^5$ (bottom 1%), and $N = 10^6$ (top 1%).

T were generated for each value of N). The close agreement between the theoretical black curve and the simulation data illustrates the accuracy of the extreme value theory estimate in formula (11).

Interestingly, the ANM curve in Figure 3 increases sharply as N increases up from $N = 10^3$ to $N = 10^5$, but the ANM curve flattens out for $N \geq 10^5$. It is notable that women with starting supplies less than $N = 10^5$ would likely face severely limited durations of ovarian function that might encroach on their ability to reproduce. On the other hand, once a woman has at least $N = 10^5$ PFs, the flattening curve in Figure 3 means that further increasing N yields much less of an increase in reproductive lifespan. Notably, $N \in [10^5, 10^6]$ is the physiological range observed in women (see below).

ANM is robust to the starting supply N

PF starting supplies at birth vary considerably between women [12]. Indeed, the mere 14 PF counts at birth given in Wallace and Kelsey [12] ranged from 1.5×10^5 to more than 10^6. A recent statistical analysis [14] of the 30 PF counts within a few months of birth reported in Wallace and Kelsey [12] found that starting supplies across a population of women are well described by a log-normal distribution with parameters

$$\mu = 12.7, \quad \sigma = 0.5 \tag{12},$$

which means

$$N = \exp(\mu + \sigma Z), \tag{13}$$

where Z is a standard normal random variable. Figure 4 shows the agreement between the distribution in formulas (12)–(13) and the starting supply data reported in Wallace and Kelsey [12] (this figure appears in the Supplementary Information of [14]). Using results on log-normal random variables, Equations (12)–(13) predict that about 1% of women have starting supplies $N \leq 10^5$ and about 1% of women have starting supplies $N \geq 10^6$.

Relative to the significant population variability in starting supply N, the ANM distribution across a population of women is curiously narrow. Indeed, the bottom 1% of the

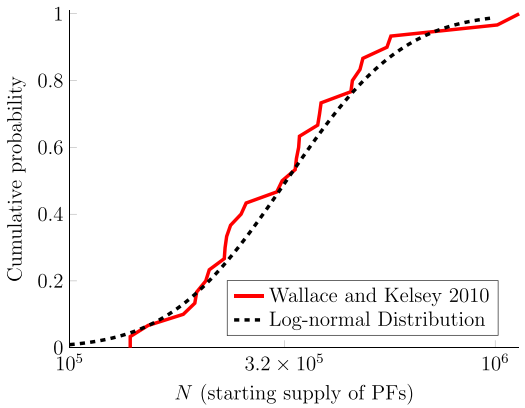

Figure 4. The PF starting supply data reported in Wallace and Kelsey [12] for females within a few months of birth (red solid curve) is well described by a log-normal distribution (black dashed curve) in formulas (12)–(13).

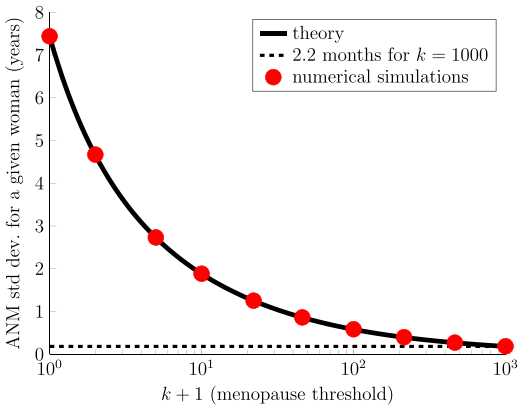

Figure 5. ANM variability for a single woman with a given starting supply N as a function of the menopause threshold. The black solid curve is the extreme value theory estimate in formula (15), which agrees with numerical simulations (red circles) of the random walk model in Johnson et al. [14]. For the physiological value of $k = 1000$, the ANM standard deviation is merely 2.2 months (black dashed line).

ANM distribution across a population is no less than 40 years and the top 1% is no greater than 60 years [32]. Hence, although N may vary by around 1000% in a population, the ANM differs by at most around 50% (i.e. around 20 years). Furthermore, the starting supply population coefficient of variation (defined as the ratio of the standard deviation to the mean) implied by formulas (12)–(13) is 53%. A commensurate population ANM coefficient of variation would mean that a sizable fraction of women would experience ovarian failure before adulthood. Instead, the actual population ANM coefficient of variation is less than 10% [33].

The relatively small population variability in ANM compared with large population variability in starting supply N can be understood as an immediate consequence of the logarithmic dependence upon N in the extreme value theory estimate of ANM in formula (11). Indeed, plugging $N = 10^5$ and $N = 10^6$ into formula (11) yields the following ANM estimates,

$$\begin{aligned} \mathbf{E}[T] &\approx 44 \text{ years}, \quad \text{if } N = 10^5, \\ \mathbf{E}[T] &\approx 58 \text{ years}, \quad \text{if } N = 10^6. \end{aligned} \tag{14}$$

Hence, though the starting supplies in equation (14) vary by an order of magnitude, the ANMs in equation (14) vary by about 30%. This point is illustrated in Figure 3. Summarizing, stochastic PFGA during postnatal life means that the physiological process of PF formation which establishes N during prenatal life need not be tightly regulated (which it evidently is not) to yield the fairly narrow ANM population distribution seen in women [28].

Oversupply yields a nearly deterministic ANM

There are multiple sources of variability in the ovarian system that could modify how ovarian aging proceeds in individuals. In the section above, we considered the impact of different starting supplies N of PFs at birth. We now consider variability stemming from stochastic PFGA.

Since the time that each PF growth-activates is stochastic, one might expect that the resulting ANM (PF depletion time) could be highly variable. However, for an individual woman with a given starting supply N and a given PFGA distribution, extreme value theory implies that the ANM T is almost deterministic. This result is a consequence of (i) the oversupply N and (ii) the menopause threshold $k \approx 10^3$.

In Figure 5, we plot the standard deviation in the ANM (denoted $\mathrm{SD}(T)$) as a function of the menopause threshold k ranging from $k = 0$ to the physiological value $k = 10^3$. In this plot, we have fixed the starting supply at the median $N = 3.2 \times 10^5$. Hence, the standard deviation plotted measures the variability from stochastic PFGA. The solid black curve is the following extreme value theory estimate (see formula (5)),

$$\mathrm{SD}(T) \approx \frac{1}{\lambda}\sqrt{\psi'(k+1)}, \tag{15}$$

where $\psi'(k+1) = \sum_{r=0}^{\infty}(r+k+1)^{-2}$ is the first-order polygamma function (we have $\sqrt{\psi'(k+1)} \approx 0.03$ for $k = 10^3$). Figure 5 shows that $\mathrm{SD}(T)$ would be quite large if k were small, with a value larger than 7 years if $k = 0$. However, Figure 5 shows that $\mathrm{SD}(T)$ is very small for k in the physiological range. Indeed, we have

$$\mathrm{SD}(T) = 2.2 \text{ months} \quad \text{if } k = 1000.$$

Summarizing, despite the stochasticity in the individual PFGA times, the oversupply ensures that the ANM is nearly deterministic for a given starting supply N and PFGA distribution.

Oversupply ensures a steady supply of growing follicles

We showed above that PF oversupply and stochastic PFGA together yield a nearly deterministic ANM. We next show that the supply of growing follicles during the reproductive lifespan is also nearly deterministic.

In Figure 6, we plot the stochastic PFGA rate per month as a function of age. For the random walk model in equation [14], the thick dashed curves are the expected PFGA rate, $-\frac{\mathrm{d}}{\mathrm{d}t}\mathbf{P}(\tau > t)$, for starting supplies $N = 3.2 \times 10^5$ (green), $N = 10^5$ (orange), and $N = 10^6$ (purple). For each starting supply, the thin curves are numbers of PFs that begin to grow each month for 10 independent stochastic simulations (representing 10 women) until only $k = 10^3$ PFs remain in the

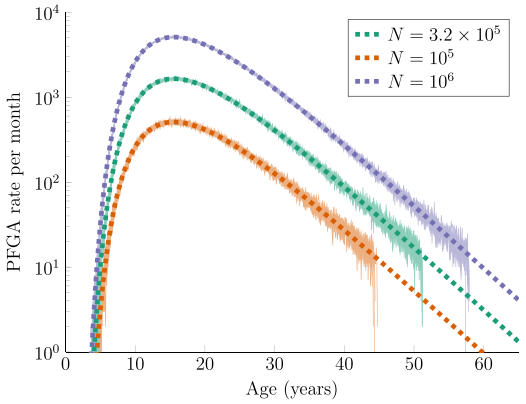

Figure 6. PFGA rate over time. The thick dashed curves are the expected PFGA rate, $-\frac{d}{dt}\mathbf{P}(\tau > t)$, for the random walk model in Johnson et al. [14] for starting supplies $N = 3.2 \times 10^5$ (median), $N = 10^5$ (bottom 1%), and $N = 10^6$ (top 1%). For each starting supply, the thin curves are numbers of PFs that begin to grow each month for 10 independent stochastic simulations (representing 10 women) until only $k = 1000$ PFs remain in the reserve.

reserve. Though these curves fluctuate stochastically around their means, they nevertheless show that there are always plenty of PFs leaving the reserve each month (i.e. tens, hundreds, or even thousands) during the reproductive lifespan until perhaps the few years before menopause.

Discussion

Women are endowed at birth with around a thousand times as many PFs as can ever be ovulated in their lifetime. This empirical fact has long been known and the apparent wastefulness of the system is often noted [10, 23–27]. In this paper, we sought to unearth possible physiological benefits of this seemingly redundant oversupply.

There is a long line of prior literature that shows that patterns of ovarian aging in mammals can be accurately described by stochastic models [10, 15–18]. However, the possible physiological source of stochasticity within the ovaries was only recently identified [14, 19, 20]. This recent work supports the hypothesis that growth behavior of primordial follicles is subject to a stochastic physiological mechanism, where physiological stress and DNA damage tend to block entrance into the cell cycle. Fluctuating ISR activity relative to a growth threshold of ISR checkpoint resolution allows stochastic PFGA, and over time, stochastic loss of PFs from the ovarian reserve endowed at birth [14]. We note here briefly that there may be other local, intra-ovarian conditions that vary stochastically over time and that may impact the behavior of PFs as we propose for the ISR pathway [14, 19].

Following this prior work [10, 14–20], our analysis here assumed that PFs leave the ovarian reserve via stochastic PFGA. We found that the average PFGA time is around 20 years or less with a standard deviation around 10 years or less. Since menopause occurs approximately when the reserve drops below 1000 PFs [1], in order to reach the population median ANM of 51 years, a woman needs 1000 PFs to last longer than their mean plus 3 standard deviations. Therefore, the vast PF oversupply at birth functions to extend the reproductive lifespan by ensuring the presence of enough PF "outliers" that stay in the reserve long enough to ensure several decades of ovarian function. In addition to this simple way to understand PF oversupply, we used extreme value theory to conclude that oversupply combined with stochastic PFGA yield robust and reliable reproductive aging.

It is interesting to consider a theoretical counter-example ovarian system that does not employ oversupply. Assuming 40 years of menstrual cycles means that roughly $40 \times 12 \approx 500$ PFs are needed for ovulation. If around 1000 additional PFs are required to maintain regular cycles [10, 11, 18, 30], then the lack of oversupply means that a woman is born with around $N = 1500$ PFs at birth. This much smaller ovarian reserve would be capable of supporting the known duration of ovarian function, but would be subject to at least two physiological constraints. First, a system lacking oversupply would require tightly regulated *intrinsic* processes to ensure that exactly the correct number of PFs leave the ovarian reserve at exactly the correct rate. If the rate of PFGA and atresia susceptibility were not tightly controlled according to genetic programs and by precise signaling, the duration of ovarian function would be highly variable. In contrast, oversupply enables a simple stochastic PFGA mechanism to yield a steady supply of growing follicles for decades. Second, any significant *extrinsic* insult could greatly compromise the reproductive lifespan for this counter-example system. For example, an exposure that damaged even 5% of ovarian follicles would result in a corresponding 5% shortening of the duration of ovarian function ($\approx$ 2.5 years in a woman who would otherwise reach the population median ANM of age 51). A more severe "catastrophic" loss of a large fraction of the ovarian reserve due to an exposure could result in the loss of ovarian function so early that the ability to reproduce would be lost.

In addition to these two constraints, the counter-example system lacking oversupply would also require a tightly regulated process for the initial formation of the PF starting supply N around the time of birth. If any fraction of the starting supply failed to develop due to aberrant events during fetal development, then the duration of postnatal ovarian function would be commensurately shortened. In particular, a system lacking oversupply but with tightly regulated processes that deplete one or a few follicles per month results in an ANM that depends roughly linearly on N. For a "catastrophic" case where 30% of the ovarian reserve fails to develop, menopause would occur by age 36 in a woman who would otherwise achieve the median ANM of 51 years (i.e. a 15 year "penalty"). In contrast, the logarithmic dependence of the ANM on N in formula (11) implied by PF oversupply and stochastic PFGA buffers the ANM from variations in N. For example, formula (11) implies that decreasing N by 30% causes the ANM to decrease by a mere 2 years. Summarizing this point, PF oversupply combined with stochastic PFGA allows the initial formation of N to be highly variable between women (which it is known to be [12, 28]) and yet yield a fairly tight ANM population distribution.

Finally, we note that the male side of human reproduction is also marked by vast redundancy. Indeed, around 10^8 sperm cells search for the egg after copulation, despite the fact that only one sperm cell fertilizes the egg [34]. Male sperm number has been understood as functioning to accelerate the search process in a manner related to the mathematical fastest first passage time [35–37]. Put another way, the excess sperm cells ensure that the first sperm cell finds the egg on a sufficiently short timescale. In the context of female folliculogenesis, we have argued that the excess PFs ensure that the last PFs to

leave the reserve leave it late enough to yield several decades of fertility, and perhaps to support health after prime fertile years in the guise of ongoing endocrine function dependent upon surviving follicles. Hence, while the oversupply of male gametes accelerates the fastest sperm cells to find the egg, the oversupply of female gametes decelerates the slowest PFs to leave the ovarian reserve.

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Supplementary Material

Supplementary Material is available at BIOLRE online.

Data Availability

Cross-sectional primordial follicle data over time from Wallace and Kelsey, 2010 [12] are available in a publicly accessible repository (Figshare) at https://doi.org/10.6084/m9.figshare.19858987.v1. Although formulas developed for data analysis are provided, computer code is available upon request.

Author Contributions

S.D.L. designed and performed mathematical analysis and computer simulations, and drafted and completed the manuscript. J.J. contributed to the design of mathematical analyses and drafted and completed the manuscript.

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