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Sporadic anovulation is not an important determinant of becoming pregnant and time to pregnancy among eumenorrheic women: a simulation study

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Abstract

Background: Attaining pregnancy is conditional upon a series of complex processes, including adequately timed intercourse, ovulation, fertilization, and implantation. Anovulation is a first line treatment target for couples with difficulty conceiving and is frequently examined in studies of fecundability.

Objectives: To identify whether sporadic anovulation is an important determinant of cumulative pregnancy rates and time to pregnancy among fertile women with regular menstrual cycles.

Methods: We simulated cumulative pregnancy rates and time to pregnancy for 12 consecutive menstrual cycles among 100,000 women based on data-driven probabilities of implantation, fertilization, ovulation, and intercourse occurring in the fertile window. We assumed anovulation probabilities of 1%, 8%, or 14.5% and intercourse averaging once per week, every other day, and daily. The model incorporated reductions in implantation and fertilization rates for successive cycles of non-pregnancy.

Results: After 12 cycles, a reduction in the per-cycle incidence of anovulation from 14.5% to 1% resulted in a 4.0% higher cumulative pregnancy rate (86.7 versus 90.7%) and similar time to pregnancy (1-cycle median difference). In contrast, increasing mean unscheduled sexual intercourse frequency from weekly to every other day was associated with a 5-cycle median reduction in time to pregnancy (weekly: 7 cycles; every other day or daily: 2 cycles) and a 28.9% increase in the cumulative pregnancy rate (weekly: 59.9%, every other day: 88.8%; daily: 91.6%).

Conclusions: In presumed fertile women with regular menstrual cycles, routine investigation of anovulation may not be an informative outcome in studies of fecundability, and routine testing to ensure ovulation and treatment of anovulation are unlikely to be medically necessary. While

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biomarkers or cervical fluid may help time intercourse to the fertile window, time to pregnancy can also be improved through increasing the frequency of unscheduled intercourse. These findings need corroboration in large preconception time to pregnancy studies.

Keywords

ovulation; embryo implantation; coitus; pregnancy rate; humans; menstrual cycle

BACKGROUND

Pregnancy is conditional upon a series of reproductive events starting with adequately timed intercourse, ovulation, fertilization of the ovum, and culminates in implantation of an embryo into a receptive endometrium. In seeking to conceive, couples frequently utilize over the counter urine luteinizing hormone (LH) tests, “ovulation predictor kits,” or other fertility indicators, such as cervical fluid, to identify ovulation and to time intercourse to conceive. Recent data suggest that these efforts may result in modestly increased fecundability (shorter times to conceive) in couples with normal fecundity.

Chronic anovulation is a common cause of infertility and may be due to polycystic ovarian syndrome or other causes. In the context of the reproductive events required for pregnancy, anovulation is often the first line treatment target for couples with difficulty conceiving[1, 2] even among women with regular menstrual cycles, and is frequently examined as an outcome of interest in studies of fecundability. However, among women who menstruate regularly and have no known subfertility, the reported per-cycle incidence of sporadic anovulation is highly variable, ranging from 1.0 to 14.5%[3–6], defined based on LH surge or luteal progesterone. Furthermore, it is unclear whether and how sporadic anovulation may impact cumulative pregnancy rates for regularly menstruating couples seeking pregnancy. To address this question, we performed a simulation study examining the impact of anovulation incidence on cumulative pregnancy rates and time to pregnancy. We compared the impact on pregnancy rates of sporadic anovulation to the impact of intercourse frequency, with the latter being arguably the most easily modifiable factor in the reproductive process for couples attempting to conceive without the use of assisted reproductive technologies.

METHODS

To examine the impact of sporadic anovulation and intercourse frequency on cumulative pregnancy rates, distributions of time to pregnancy were simulated over 12 menstrual cycles among a population of 100,000 women attempting to conceive. To do this, we first constructed a mathematical model that characterized the underlying biological processes (e.g. intercourse, ovulation, fertilization, implantation) and then used estimates from the literature to derive reasonable estimates for each parameter involved in the pathway to pregnancy. We then simulated pregnancy rates after 6 and 12 months based on these data-driven parameters.

Relationships among parameters required for pregnancy

Attainment of a pregnancy is conditional upon a series of reproductive events starting with adequately timed intercourse, ovulation, fertilization of the ovum, and culminating in implantation of an embryo into the uterine lining, which is observable via the embryo's secretion of human chorionic gonadotropin (hCG) into maternal circulation. The reproductive milestones required for pregnancy each have a probability of success, some being conditional on prior events[7], and can be represented using the following equations as a simple model of this series of complex biological processes.

Since

$$P(implantation) = P(implantation \mid fertilization = 1)P(fertilization),$$

$$P(fertilization) = P(fertilization \mid sex = 1,\ ovulation = 1)P(sex\ \&\ ovulation),$$

$$P(sex\ \&\ ovulation) = P(sex)P(ovulation)\,.$$

We can obtain:

$$P(implantation) = P(implantation \mid fertilization = 1)P(fertilization \mid sex = 1,\ ovulation = 1)\ P(sex)P(ovulation), \quad \text{Equation 1}$$

Adequately timed intercourse, its probability represented by *P*(sex) in Equation 1, is defined as a female-male couple having intercourse within the approximate 6-day fertile window[8, 9], beginning ~5 days prior to ovulation and ending on the day of ovulation[10]. Ovulation, its probability represented by *P*(ovulation), consists of maturation of at least one ovarian follicle, with release of viable oocyte into the oviduct[11, 12]. The release of a viable oocyte will be approximated using hormonal assessment of ovulation detection (LH surge or luteal progesterone). We describe the implications of this approximation in the Comment. Fertilization of the ovum can only occur if there is ovulation and adequately timed intercourse with a fertile male, the conditional probability denoted by *P*(fertilization|sex=1, ovulation=1). Similarly, implantation of the embryo into the endometrium can only happen if there is fertilization, represented as *P*(implantation|fertilization=1). For the purposes of this paper, the event of a new pregnancy is synonymous with implantation, clinically observable by the detection of hCG in maternal serum or urine. The probability of pregnancy (i.e., *implantation*) is modeled as the product of *implantation given fertilization*, *fertilization given sex and ovulation*, *sex*, and *ovulation*, shown in Equation 1. For the purposes of this simulation, we assume that each of the mathematical probabilities in Equation 1 are statistically and empirically independent of one another[13]. In a fecund population, this assumption likely holds, though we describe the implications of this assumption in the Discussion.

Simulation setup: parameter derivation

Probabilities used for parameters on the right-hand side of Equation 1 were based on existing literature[14] and the relations required by the equation (Table 1 **- Derivation**).

Anovulation—Given the previously stated range of sporadic anovulation among reproductive aged women (1–14.5%[3–6]), we performed simulations across this range, at 1% and 14.5%, as well as at the approximate mid-point of this range (8%).

Sex and implantation—Among couples assumed to be fertile, the maximum probability of attaining pregnancy is approximately 38% from intercourse occurring on peak day fertility (i.e., sexual intercourse that always occurs in the fertile window), as documented by Stanford et al[15]. Meanwhile, the usual probability of pregnancy has been shown to be approximately 30% among fertile couples attempting conception (i.e., when intercourse occurs within the 6-day fertile window in 95% of cycles), as reported by Wilcox et al[16]. We used both relations in our simulations to examine the robustness of our findings.

Implantation given fertilization—*Implantation given fertilization* and *fertilization given sex and ovulation* are not directly observable outside of assisted reproductive technologies. However, the probability of *implantation given fertilization* in the setting of embryos transferred after IVF for women less than 35 years of age has been reported to be in the range of 45–70%[17]. We expected this probability for natural (i.e. *in vivo*) conceptions to be on the higher end of these ranges (e.g., 70%) due to the population being of normal fecundity and fertilization occurring in the more natural environment of the oviduct.

Fertilization given sex and ovulation—In Scenario 1, we used parameters from Stanford et al[15] relating the relationship between *sex* occurring in the fertile window (100%) and *implantation* (38%) and plausible values of the other parameters (*anovulation* = 8%, and *implantation given fertilization* = 70%) to calculate the probability of *fertilization given sex and ovulation* as 59% using Equation 1. In Scenario 2, we used parameters based on Wilcox et al (*sex* = 95%, *implantation* = 30%)[16] to calculate the probability of *fertilization given sex and ovulation* using Equation 1, resulting in 49% (Table 1 **- Derivation**). A meta-analysis of IVF cycles without ICSI (i.e., oocyte immersed in media with sperm) for unexplained infertility reported a 75–95% oocyte fertilization rate (*fertilization given sex and ovulation*)[18]. Fertilization rates are expected to be lower in the setting of attempted natural conception, given the need for successful sperm transport and capacitation that are bypassed in IVF, so the calculated probabilities of 49% and 59% were assumed to be plausible in the setting of natural conceptions.

Intercourse frequency and sex—Assuming the fertile window is unknown, intercourse averaging overall as once per week, every other day, and every day has been estimated to result in pregnancy probabilities of 15%, 33%, and 37% respectively[16]. Using Equation 1 with *anovulation* = 8%, *fertilization given sex and ovulation* = 59%, and *implantation given fertilization* = 70%), these overall average intercourse frequencies translated to a probability of sex occurring in the fertile window of 39%, 87%, and 97%, respectively. Here, we see that intercourse occurring on average, every other day and daily did not result in a probability of *sex* = 1.0 (e.g. less than 100% probability), as frequency is averaged across the menstrual cycle, and may be impacted by biology (e.g., variations in numbers of viable sperm in an ejaculation) and/or social and behavioral influences on the probability of intercourse[19].

Statistical Analysis

We simulated the presence or absence of each of the events required for pregnancy described above. For each cycle, if all requisite events were simulated to have occurred, and accordingly pregnancy was calculated as having occurred, then individuals attaining pregnancy were removed from remaining menstrual cycles of observation.

For our primary analysis examining the impact of the varying reported incidence of sporadic anovulation, three sets of time to pregnancy distributions were simulated based on *anovulation* = 1%, 8%, or 14.5%, *implantation given fertilization* = 70%, *sex* = 87%, the latter corresponding to intercourse occurring every other day. *Fertilization given sex and ovulation* was set to either 59% or 49%, derived from Stanford[15] or Wilcox[16], respectively. For simulations examining the secondary comparative impact of intercourse frequency, three distributions were calculated based on *sex* = 39%, 87%, or 97% and *anovulation* = 8%, *fertilization given sex and ovulation* = 59%, *and implantation given fertilization* = 70% (Table 1 **- Analysis**). To reflect the lower fecundability among the remaining pool of non-pregnant women with each successive cycle of observation, relative reductions of 7.5% were implemented for *implantation given fertilization* and *fertilization given sex and ovulation* for each successive cycle of non-pregnancy, which yielded cumulative pregnancy rates consistent with reported infertility rates of 7.4[20] to 15%[21] in the U.S. For each of these time to pregnancy distributions, cumulative pregnancy rates were quantified after 6 and 12 menstrual cycles of attempting pregnancy. For analyses examining the impact of sporadic anovulation, fecundability odds ratios (FORs) were calculated for 1% and 8% anovulation relative to 14.5% anovulation, and for analyses examining the impact of intercourse frequency, FORs for intercourse averaging every other day and daily were calculated relative to weekly intercourse.

Ethics Approval

As data were simulated, the current data are not based on a clinical study protocol and Institutional Review Board approvals do not apply.

RESULTS

Impact of anovulation on cumulative pregnancy rates and time to pregnancy

Changing per-cycle anovulation incidence between 1% and 14.5% had no appreciable impact on cumulative pregnancy rates in Scenario 1[15] or Scenario 2[16]. Cumulative pregnancy rates were slightly lower under Scenario 2, but overall patterns were similar. Time to pregnancy survival curves remained close over the 12 cycles of follow-up (Figure 1 and eFigure 1).

In Scenario 1[15], cumulative pregnancy rates after 12 cycles for 1%, 8%, and 14.5% anovulation incidence were 90.7%, 88.8%, and 86.7%, respectively, for an absolute difference of 4.0% between 1% to 14.5% anovulation (Table 2). The difference in cumulative 6-cycle pregnancy rate between 1% and 14.5% anovulation was expectedly slightly higher, at 5.4% (82.7% vs 77.3%). Anovulation incidence of 14.5% was associated with a 1-cycle median reduction in time to pregnancy compared to 8% or 1% incidence (14.5%: 3 cycles; 8% or 1%: 2 cycles). Compared to 14.5% anovulation, FORs for 8% and 1% anovulation were 1.21 and 1.49, respectively, after 12 cycles of follow-up.

Assessing the robustness of these findings to a different relationship between *sex* and *implantation*[16], Scenario 2 produced 12-cycle cumulative pregnancy rates of 85.5%, 83.2%, and 80.7% for *anovulation* incidence of 1%, 8%, and 14.5%, respectively, leading to an absolute difference of 5.2% between 1% and 14.5% anovulation (eTable 1 and eFigure 1). The difference in cumulative 6-cycle pregnancy rate between 1% and 14.5% anovulation was similar, at 5.8% (75.7% vs 69.9%). Anovulation incidence of 14.5%, 8%, and 1% were each associated with a median time to pregnancy of 3 cycles. Compared to 14.5% anovulation, FORs for 8% and 1% anovulation were 1.18 and 1.41, respectively, after 12 cycles of follow-up.

Impact of intercourse on cumulative pregnancy rates and time to pregnancy

In contrast, cumulative pregnancy rates varied widely by frequency of unscheduled intercourse. Specifically, cumulative pregnancy rates after 12 cycles were 59.9% for untimed weekly intercourse, 88.8% for every other day, and 91.6% for daily, contributing to an absolute difference of 28.9% when average intercourse pattern increased from weekly to every other day (Table 3). The difference in cumulative 6-cycle pregnancy rate between intercourse occurring weekly to every other day was 30.3% (80.0% vs 48.7%). Time to pregnancy survival curves for every other day and daily intercourse tracked closely, while the survival curve for weekly intercourse tracked noticeably lower (Figure 2). Intercourse averaging weekly was associated with a 5-cycle median reduction in time to pregnancy compared to intercourse averaging every other day or daily (weekly: 7 cycles; every other day or daily: 2 cycles).

Compared to intercourse averaging weekly, FORs for intercourse averaging every other day and daily were 5.28 and 7.28, respectively, after 12 cycles of follow-up.

We observed similar patterns across ranges of all parameters reported in the literature (eTable 2). In particular, we see that cumulative pregnancy rates are nearly identical whether we assume that *fertilization | sex & ovulation* is higher or lower in the setting of attempted natural conceptions, as an increase in *fertilization | sex & ovulation* requires *implantation | fertilization* to be proportionally lower.

COMMENT

Principal findings

Large differences in the probability of sporadic anovulation as has been reported in prior literature resulted in small changes in cumulative pregnancy rates and time to pregnancy, whereas intercourse frequency produced substantially larger changes. While anovulation is frequently examined in studies of fecundability and is a first line treatment target for couples with difficulty conceiving, these simulations highlight that sporadic anovulation in regularly menstruating women is not an important determinant of time to pregnancy. Given the similar cumulative pregnancy rates observed across the simulated range of sporadic anovulation incidence, previously reported estimates for its incidence are likely similarly plausible.

Strengths of the study

For each event requisite to pregnancy, we used empirical probabilities to understand the impact of anovulation across its reported spectrum of incidence on cumulative pregnancy rates and time to pregnancy. Our finding that anovulation does not meaningfully impact time to pregnancy or cumulative pregnancy rate was consistent across ranges of plausible values for each event requisite to pregnancy (Equation 1), within the bounds of literature-based rates for fecund couples. Since the probabilities of *implantation given fertilization* and *fertilization given sex and ovulation* are not directly observable among *in vivo* conceptions in humans or animal models[22], we have benchmarked with observed measurements from IVF. We can logically expect that the higher end of the range for implantation and the lower end of the range for fertilization in couples receiving IVF may reflect their values in fecund couples. However, as shown in eTable2, findings are not contingent upon this assumption, as the joint probability of *implantation given fertilization* and *fertilization given sex and ovulation* is fixed by Equation 1 given *implantation* and *sex* (relationship prescribed in Scenario 1[15] or in Scenario 2[16]), and *anovulation* (1–14.5%[3–6]).

Limitations of the data

Since we assumed sporadic anovulation within fecund populations to be representative of normal reproductive function, we believe the assumption of independence of all probabilities in Equation 1 to be a reasonable and likely approximation for the purposes of this simulation. For example, a prior study found no relationship between intercourse frequency and anovulation among sexually active women[23], justifying the independence between *sex* and *ovulation*. While independence of all parameters may be a simplification of the underlying biological mechanism, it is reassuring that our model generates results congruent with observed cohort data for time to pregnancy studies[24–26].

This simulation is only generalizable to fecund couples with regularly menstruating women since the etiology of sporadic anovulation likely differs from chronic disorders such as polycystic ovarian syndrome. Specifically, there is likely dependence between probabilities in Equation 1: anovulation could be correlated with suboptimal fertilization or endometrial receptivity for implantation[27], and common comorbidities such as obesity and hyperandrogenism may impact pregnancy rates[28–30]. Further, polycystic ovarian syndrome is characterized by much higher anovulation incidence than examined in this simulation as a result of long or absent menstrual cycles, which is distinct from sporadic anovulation with typical menstrual cycle length and regular menstruation.

Interpretation

While we have defined ovulation as “maturation of at least one ovarian follicle, with release of viable oocyte into the oviduct”, we utilized anovulation incidence estimates based hormonal assessment rather than direct assessment using transvaginal ultrasonography. Using hormonal assessment, reported incidence of sporadic anovulation among women who menstruate regularly and without known subfertility has ranged from 1.0 to 14.5%[3–6]. These estimates are impacted by normal variation in the strength of the endocrine signals of the ovulation stimulus that are relied upon for ovulation detection (i.e. LH surge or luteal progesterone)[31], and are impacted by the algorithm used to interpret the available data[32]. Hormonal assessment is more prevalent than transvaginal sonographic assessment due to practical and cost considerations associated with using transvaginal sonography in large cohorts of women, and over consecutive menstrual cycles. However, LH surge or luteal progesterone assessment may overestimate the incidence of true anovulation by including suboptimal ovulation. There may be a continuum in the quality of ovulation, whereby sporadic anovulation may be associated with altered and diminished ovulatory quality when ovulation does occur[31]. For instance, a study examining 250 women each for 2 menstrual cycles reported lower serum sex steroids in the ovulatory cycles of women who also had one anovulatory cycle compared to women with two ovulatory cycles[3]. A dose–response was reported in progesterone levels, the highest among women with two ovulatory cycles, followed by those with one ovulatory and one anovulatory cycle, followed by those with two anovulatory cycles. The incidence of true anovulation may be on the lower end of the reported range of 1.0 to 14.5%, as evidenced by a single anovulatory cycle detected by transvaginal sonography among 150 cycles in 53 women[33], while higher estimates up to 14.5% may have an increased propensity for including suboptimal ovulation. Nevertheless, sporadic anovulation estimates of 1% produced similar findings regarding the impact of intercourse frequency (eTable 2). Further, we find that anovulation incidence across this broad reported range are likely similarly plausible among fecund couples given reported rates of other steps of the reproductive process.

While sporadic anovulation did not produce remarkable differences in cumulative pregnancy rates, substantial differences did emerge by frequency of intercourse, underscoring the importance of frequency and its relationship to timing within the fertile window. Without having knowledge of the fertile window, intercourse averaging every day or every other day both translated to sex occurring within the fertile window for most cycles (sex = 0.97 and 0.87, respectively). Since these are average intercourse frequencies, these probabilities are relevant for a variety of specific intercourse patterns. These probabilities do not require a constant frequency of intercourse throughout the menstrual cycle, as intercourse may naturally occur more frequently within the fertile window[34], even without specific knowledge of when it occurs.

Though the body of existing data on the impact of timed intercourse are insufficient to draw conclusions[35], recent observational studies and a trial in couples trying to conceive suggest that timing of intercourse to the fertile window using fertility indicators, results in higher fecundability independent of coital frequency, further highlighting the importance of intercourse timing[36–38]. A recent study that found that double intrauterine insemination with donor sperm did not increase ongoing pregnancy rates in women without a history of infertility provides additional evidence supporting that increasing frequency matters to cover the fertile window, but does not improve pregnancy rates once the fertile window is already attained[39].

Our simulation supports the principle that unscheduled regular intercourse, averaging every other day, will greatly increase the chances of intercourse occurring within the fertile window, which will in turn improve time to pregnancy. However, for a variety of personal reasons, some couples of normal fecundity[35, 37, 38] may find timing of intercourse to the fertile window a more acceptable approach to increase fecundability, e.g., among women who experience pain with intercourse. An additional caveat for the strategy of frequent unscheduled intercourse is that one study has suggested that frequent intercourse in the peri-implantation time window may reduce fecundability[40], though this finding has not yet been confirmed.

CONCLUSIONS

This study provides evidence that sporadic anovulation does not seem to be an important determinant of time to pregnancy in healthy, regularly cycling populations of women attempting to conceive. Accordingly, routine investigation of sporadic anovulation in regularly cycling women may not be warranted in studies of fecundability, though previously reported estimates for its incidence are likely similarly plausible. Similarly, routine testing to ensure ovulation and treatment of anovulation are unlikely to be medically necessary among women with regular menstrual cycles and without a history of subfertility. While biomarkers such as urinary luteinizing hormone or cervical fluid may be useful for precise timing of intercourse to the fertile window, time to pregnancy can also be improved through unscheduled frequent intercourse. We encourage large preconception time to pregnancy studies to seek validation of the current findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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In presumed fertile women with regular menstrual cycles, routine investigation of anovulation may not be an informative outcome in studies of fecundability, and routine testing to ensure ovulation and treatment of anovulation are unlikely to be medically necessary.

Synopsis

Study question:

Is sporadic anovulation an important contributor to cumulative pregnancy rates and time to pregnancy among fertile women with regular menstrual cycles?

What's already known:

Anovulation is a first line treatment target for couples with difficulty conceiving and is frequently examined in studies of fecundability.

What this study adds:

In a data-driven simulation of 12 consecutive menstrual cycles, large differences in sporadic anovulation did not produce important differences in cumulative pregnancy rates or time to pregnancy. This study provides evidence that in presumed fertile women with regular menstrual cycles, routine investigation of anovulation may not be an informative outcome in studies of fecundability, and routine testing to ensure ovulation and treatment of anovulation are unlikely to be medically necessary.

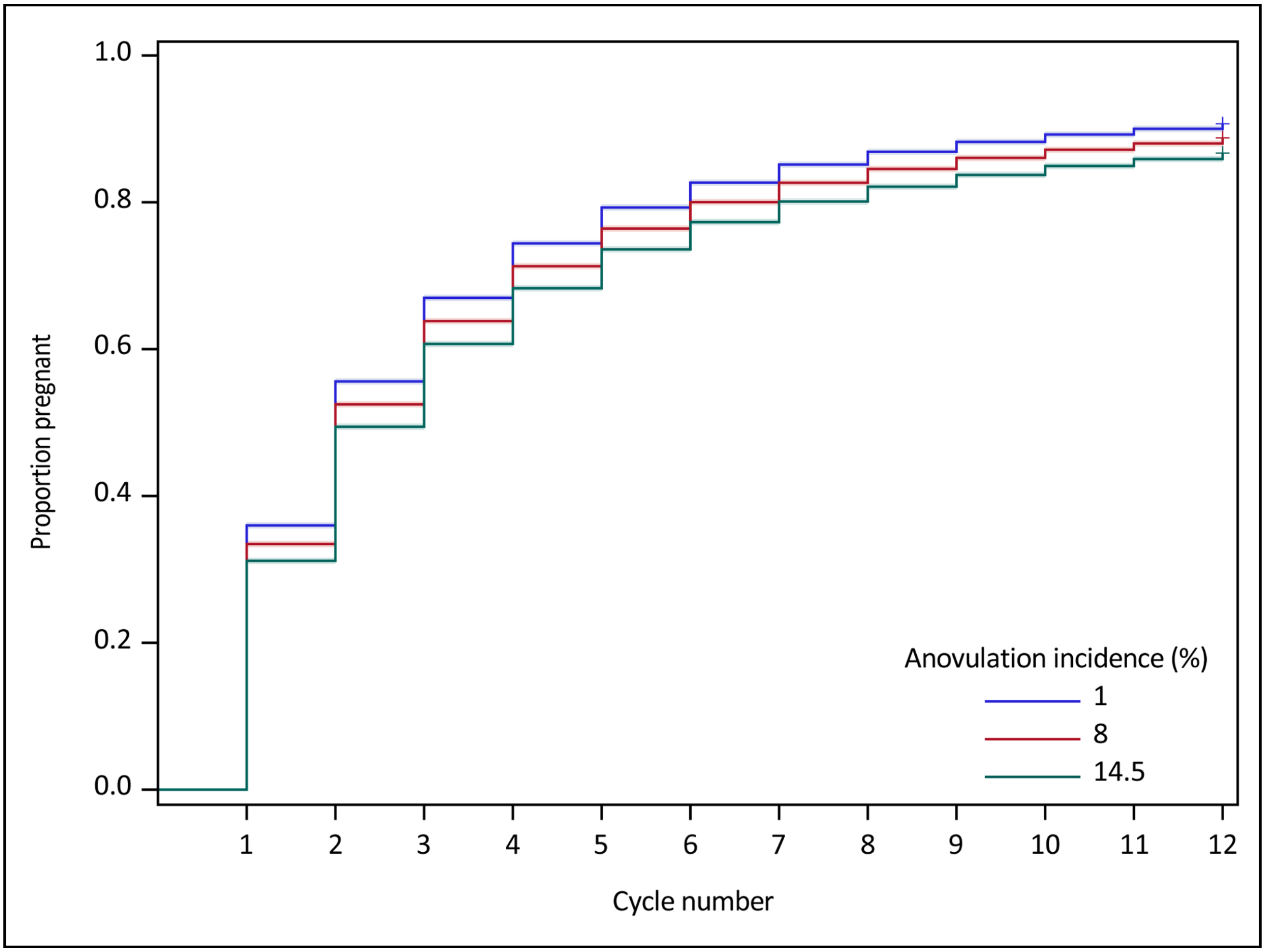

Figure 1.

Survival curves and 95% Hall-Wellner confidence bands comparing sporadic anovulation rates of 1%, 8%, and 14.5% on simulated time to pregnancy over 12 cycles of follow-up among 100,000 women[a,b]

[a] *Sex* in the fertile window set equal to 87% for each cycle of observation; *implantation given fertilization* = 70% and ***fertilization given sex and ovulation*** = **59%** for the first cycle of observation, followed by a 7.5% reduction per cycle for *implantation given fertilization* and *fertilization given sex and ovulation*; probability of *implantation* calculated using Equation 1.

[b] Scenario 1 relationship between *sex* and *implantation*: among fecund couples attempting conception, the maximum probability of attaining pregnancy is ~38% when sexual intercourse always occurs in the fertile window (*sex* = 1.0)[15].

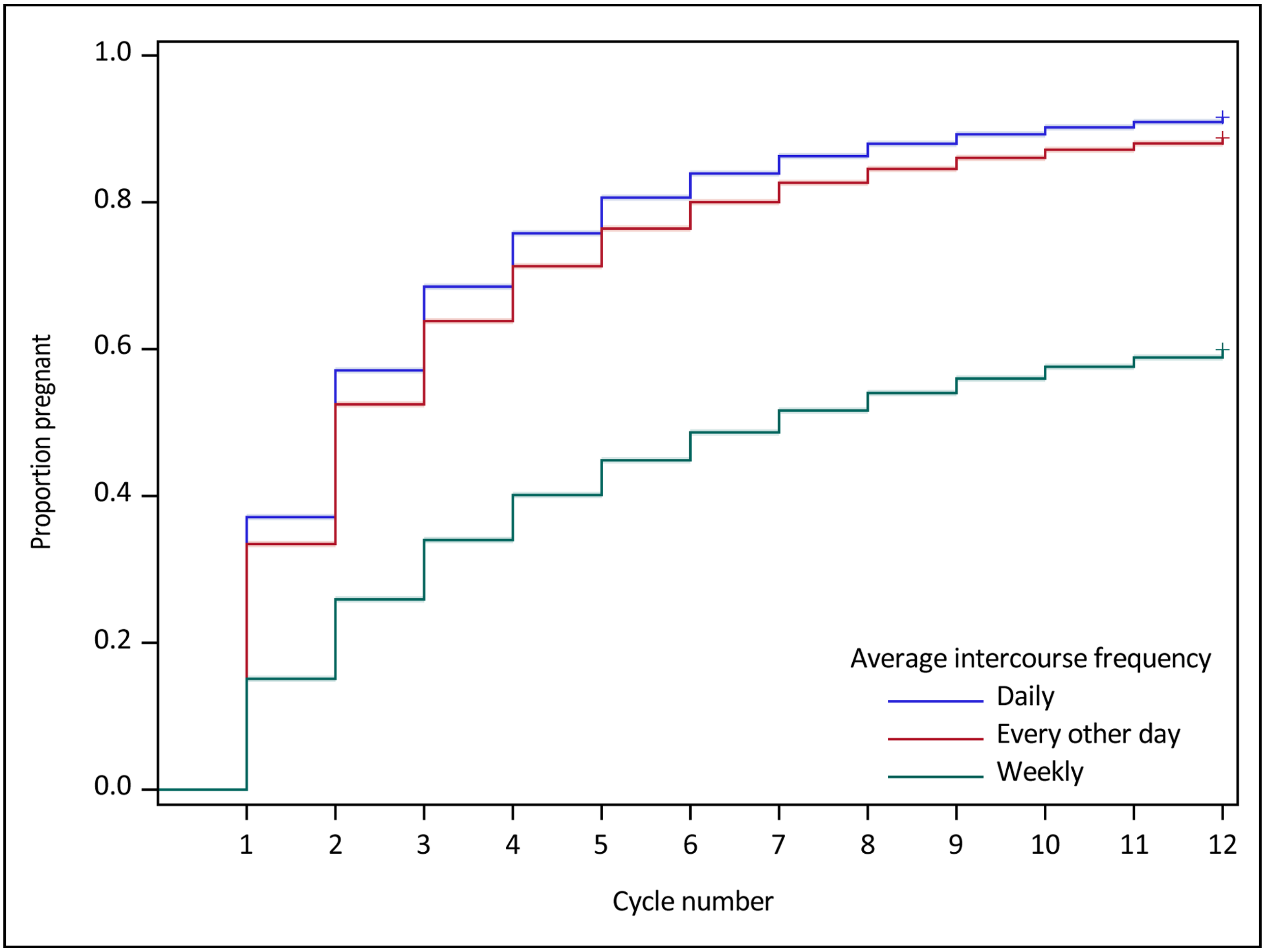

Figure 2.

Survival curves and 95% Hall-Wellner confidence bands comparing weekly, every other day, and daily intercourse on simulated time to pregnancy over 12 cycles of follow-up among 100,000 women[a,b]

[a] *Anovulation* set equal to 8% for each cycle of observation; probability of i*mplantation*|*fertilization* = 70% and probability of *fertilization*|*sex & ovulation* = 59% for the first cycle of observation, followed by a 7.5% reduction per cycle for i*mplantation*|*fertilization* and *fertilization*|*sex & ovulation*; probability of *implantation* calculated using Equation 1

[b] Scenario 1 relationship between *sex* and *implantation*: among fecund couples attempting conception, the maximum probability of attaining pregnancy is ~38% when sexual intercourse always occurs in the fertile window (*sex* = 1.0)[15].

Table 1.

Parameters used in derivation of *Fertilization / sex & ovulation* and parameters used in analyses

	Derivation		Analysis		
			Varying sporadic anovulation		Varying intercourse frequency
Parameter	**Scenario 1**[15]	**Scenario 2**[16]	**Scenario 1**[15]	**Scenario 2**[16]	
Implantation	38%	30%	*Simulated*	*Simulated*	*Simulated*
Anovulation	8%	8%	1, 8, 14.5%	1, 8, 14.5%	8%
Implantation / fertilization	70%	70%	70%	70%	70%
Fertilization / sex & ovulation	*Calculated* 59%	*Calculated* 49%	59%	49%	59%
Sex	100%	95%	87%	87%	38, 87, 97%

Table 2.

Comparison of sporadic anovulation rates of 1%, 8% and 14.5% on simulated time to pregnancy and fecundability odds ratios[a] over 12 cycles of follow-up in a cohort of 100,000 women[b] (using Scenario 1[c] relationship between *sex* and *implantation*)

Cycle	***anovulation* = 14.5%** Population at risk	% becoming pregnant	Cumulative pregnancy rate (%)	***anovulation* = 8%** Population at risk	% becoming pregnant	Cumulative pregnancy rate (%)	FOR[d]	***anovulation* = 1%** Population at risk	% becoming pregnant	Cumulative pregnancy rate (%)	FOR[d]
1	100,000	31.2	31.2	100,000	33.5	33.5	1.11	100,000	36.0	36.0	1.24
2	68,827	26.5	49.4	66,544	28.6	52.5	1.13	64,008	30.6	55.6	1.28
3	50,559	22.3	60.7	47,526	23.9	63.8	1.14	44,399	25.6	67.0	1.31
4	39,301	19.3	68.3	36,190	20.7	71.3	1.15	33,015	22.5	74.4	1.35
5	31,705	16.7	73.6	28,699	17.9	76.4	1.16	25,598	19.1	79.3	1.37
6	26,408	14.1	77.3	23,572	15.2	80.0	1.18	20,698	16.4	82.7	1.40
7	22,690	12.3	80.1	19,982	13.2	82.7	1.18	17,312	14.2	85.1	1.42
8	19,901	10.1	82.1	17,343	10.9	84.6	1.19	14,857	11.7	86.9	1.44
9	17,883	9.1	83.7	15,455	9.7	86.0	1.20	13,126	10.4	88.2	1.46
10	16,261	7.4	85.0	13,963	8.0	87.2	1.20	11,761	8.5	89.2	1.47
11	15,051	6.3	85.9	12,842	6.7	88.0	1.21	10,761	7.2	90.0	1.48
12	14,102	5.7	86.7	11,977	6.3	88.8	1.21	9,985	6.9	90.7	1.49

[a]Fecundability odds ratios for 1% and 8% anovulation calculated relative to 14.5% anovulation

[b]*Sex* in the fertile window set equal to 87% for each cycle of observation; *implantation given fertilization* = 70% and ***fertilization given sex and ovulation* = 59%** for the first cycle of observation, followed by a 7.5% reduction per cycle for *implantation given fertilization* and *fertilization given sex and ovulation*; probability of *implantation* calculated using Equation 1.

[c]Scenario 1: among fecund couples attempting conception, the maximum probability of attaining pregnancy is ~38% when sexual intercourse always occurs in the fertile window (*sex* = 1.0)[15].

[d]Fecundability Odds Ratio

Table 3.

Comparison of intercourse averaging weekly, every other day, and daily on simulated time to pregnancy and fecundability odds ratios[a] over 12 cycles of follow-up in a cohort of 100,000 women[b] (using Scenario 1[c] relationship between *sex* and *implantation*)

	Weekly			Every other day				Daily			
Cycle	Population at risk	% becoming pregnant	Cumulative pregnancy rate (%)	Population at risk	% becoming pregnant	Cumulative pregnancy rate (%)	FOR[d]	Population at risk	% becoming pregnant	Cumulative pregnancy rate (%)	FOR[d]
1	100,000	15.1	15.1	100,000	33.5	33.5	2.83	100,000	37.1	37.1	3.32
2	84,900	12.7	25.9	66,544	28.6	52.5	3.16	62,873	31.8	57.1	3.80
3	74,083	10.9	34.0	47,526	23.9	63.8	3.42	42,900	26.6	68.5	4.22
4	66,000	9.3	40.1	36,190	20.7	71.3	3.71	31,499	23.1	75.8	4.67
5	59,868	7.9	44.9	28,699	17.9	76.4	3.98	24,222	20.1	80.6	5.12
6	55,132	6.9	48.7	23,572	15.2	80.0	4.22	19,364	17.0	83.9	5.51
7	51,335	5.8	51.7	19,982	13.2	82.7	4.46	16,070	14.7	86.3	5.89
8	48,352	4.9	54.0	17,343	10.9	84.6	4.66	13,713	12.2	88.0	6.22
9	45,974	4.3	56.0	15,455	9.7	86.0	4.84	12,035	10.7	89.3	6.52
10	44,004	3.6	57.6	13,963	8.0	87.2	5.00	10,749	8.8	90.2	6.78
11	42,401	3.0	58.9	12,842	6.7	88.0	5.14	9,799	7.4	90.9	7.01
12	41,141	2.6	59.9	11,977	6.3	88.8	5.28	9,069	7.2	91.6	7.28

[a] Fecundability odds ratios for every other day and daily calculated relative to weekly intercourse

[b] *Anovulation* set equal to 8% for each cycle of observation; probability of i*mplantation|fertilization* = 70% and probability of *fertilization|sex & ovulation* = 59% for the first cycle of observation, followed by a 7.5% reduction per cycle for i*mplantation|fertilization* and *fertilization|sex & ovulation*; probability of *implantation* calculated using Equation 1.

[c] Scenario 1: among fecund couples attempting conception, the maximum probability of attaining pregnancy is ~38% when sexual intercourse always occurs in the fertile window (*sex* = 1.0)[15].

[d] Fecundability Odds Ratio