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Clustering of retrospectively-reported and prospectively observed time-to-pregnancy

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Abstract

Purpose—Given reportedly high clustering but limited validity of retrospectively-reported time-to-pregnancy (TTP), we assessed within-woman clustering for retrospectively-reported TTPs alone and including gold-standard prospectively observed TTPs among women with 2 retrospectively-reported and 1 prospectively observed TTPs. We further investigated whether past trying times inform future trying time among women with 1 retrospectively-reported and 1 prospectively observed TTPs.

Methods—501 couples attempting pregnancy were prospectively observed until hCG pregnancy or 12 months of trying. Women reported TTP for past planned pregnancies. Clustering as measured by the frailty variance was estimated using discrete Cox frailty models, adjusted for age, BMI, smoking at each attempt. Utility of past attempts to inform future attempts was assessed with discrete Cox models and relative risk regression, adjusted for baseline age, BMI, smoking.

Results—75 women with 2 prior pregnancies contributed 180 retrospective and 91 prospective TTPs for frailty modeling. Retrospectively-reported TTP clustering was high (frailty variance=0.89) but substantially lower when including prospectively observed TTPs (frailty variance=0.42). Among 202 women with 1 prior pregnancies, past trying times did not inform future trying time.

Conclusions—TTP recall rather than TTP may account for clustering. Past trying times may not inform future trying times.

Keywords

time-to-pregnancy; fecundity; conception; conception delay

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Introduction

Several reproductive outcomes cluster within women, including pregnancy loss, preterm birth, preeclampsia, and gestational diabetes (1–6), and women’s prior outcomes are often used to inform likelihood of future occurrence. Time-to-pregnancy (TTP), defined as the number of cycles or months of unprotected sexual intercourse required to achieve pregnancy, also reportedly clusters within women (7, 8). Two previous studies using retrospectively-reported TTP among fertile women in Europe and the US reported high TTP clustering (7, 8). In contrast, using data from a US preconception cohort with prospective TTP measurement, clustering was low among women experiencing pregnancy loss (9).

Given these reported differences in TTP clustering by method of TTP ascertainment, we evaluated TTP clustering among a unique cohort of women with information on both retrospectively-reported and prospectively observed TTPs. We investigated the extent of TTP clustering within women for retrospectively-reported TTPs alone and including gold-standard prospectively observed TTPs for women with 2 retrospectively-reported and 1 prospectively observed TTPs. We further investigated whether retrospectively-reported trying times informed prospectively observed trying time for women with 1 retrospectively-reported and 1 prospectively observed TTPs.

Material and methods

Study population

The Longitudinal Investigation of Fertility and the Environment (LIFE) Study is a population-based, preconception cohort of 501 couples recruited upon discontinuing contraception to try for pregnancy and followed for 12 months of trying (10). Couples experiencing pregnancy loss were able to continue in the study allowing for measurement of subsequent TTPs; couples not pregnant after 12 months were censored. The inclusive study design only excluded couples with clinically diagnosed infertility/sterility. Inclusion criteria comprised couples in a committed relationship, intending to begin pregnancy attempts or off contraception for 2 months, partners communicate in English or Spanish, men aged 18-years-old and women aged 18-40-years-old, menstrual cycle lengths between 21–42 days, and no past year use of injectable contraceptives. Institutional Review Board approval was obtained from all participating institutions; informed consent was obtained from all participants prior to data collection.

At enrollment, women were queried on their medical, social, and reproductive histories. Particularly, women were asked about each previous pregnancy including age at pregnancy, whether pregnancy was planned, TTP for planned pregnancies, and pregnancy outcome(s). Women were asked if they currently smoked and ages they started and stopped smoking cigarettes, if applicable. They provided their weight for 5-year intervals from 15-years-old until baseline. Height and weight were measured upon enrollment, and women were given and instructed in the use of the urine-based ClearBlue™ Easy digital fertility monitor. These monitors provide valid measures of ovulation (11) to help couples time intercourse relative to impending ovulation. Women were provided with highly sensitive (25 IU/L)

urine-based ClearBlue™ Easy digital home pregnancy tests to facilitate ascertainment of pregnancies. A single positive pregnancy test on day of expected menstruation denoted an hCG pregnancy.

Measures

Prospectively observed menstrual cycles were used to measure TTP during the study as retrospectively-reported TTP has limited validity relative to prospective measurement (12). At enrollment, women were administered a home pregnancy test to ensure they were not pregnant. Time couples were off contraception prior to study entry (7% one and 15% two months) was accounted for in analysis of TTP. For these analyses, we assume that months and cycles are equivalent. Median observed cycle length was 30 days (interquartile range (IQR)=27–35). Conception delay was defined as TTP>6.

Other factors relevant to TTP that may change between pregnancy attempts include maternal age, body mass index (BMI), and smoking status (13–16); therefore, these were included as covariates in modeling. For attempts during the study, age, measured BMI, and self-reported smoking status at enrollment were used. For pregnancies occurring before study entry, reported age at pregnancy was used. If a woman's reported age at pregnancy fell in the interval during which she reported smoking cigarettes, she was considered a smoker for that attempt. A woman's height at enrollment was considered fixed for all pregnancies and her self-reported weight in the 5-year interval corresponding to the age at which she reported her pregnancy was used to calculate BMI. Pregnancy loss included losses reported during the baseline interview (i.e., miscarriage, stillbirth, or ectopic).

Statistical analysis

Summary statistics of the sample were conducted using differences in TTP between first prospectively observed attempt and the mean of all retrospectively-reported TTPs and computing sensitivity, specificity, positive and negative predictive values (PPV, NPV) of past conception delay for prospective conception delay.

Discrete Cox frailty models with lognormal frailty distribution were used to estimate TTP clustering as measured by the frailty variance (8) for women with 2 retrospectively-reported TTP (n=75). These models incorporate a frailty variable, which is akin to a random effect, to quantify the degree of within-woman dependency in TTP due to unobserved factors (e.g. after adjustment for covariates) and yield standard errors (SE) for the frailty variance. Higher frailty variance indicates higher within-woman TTP clustering. Separate models were constructed for retrospectively-reported TTP only and retrospectively-reported with prospectively observed TTP; all adjusted for age, BMI, and smoking at each attempt. When including both retrospectively-reported and prospectively observed TTPs, models included a strata statement for TTP type and a TTP type*BMI interaction term (17). A bootstrap approach was used to test difference in frailty variances between models based on overlapping subgroups of women. 500 bootstrap samples of 75 women each were resampled from the original data and frailty models were run for each of these samples and a percentile based 95% confidence interval for the difference in the frailty variance for each pair of models was calculated (18).

To determine if estimates varied by recall period, we ran frailty models restricted to all prospective attempts and retrospective pregnancies within 3, 6, and 10 years of enrollment. These cutoffs reflect 40%, 80%, and 90% of past pregnancies for women with 2 retrospectively-reported TTP. We also assessed clustering of all retrospective attempts with only the first prospective attempt as only women with observed losses had multiple prospective attempts.

For women with 1 retrospectively-reported TTP (n=202), we assessed whether retrospectively-reported TTP or conception delay may inform prospectively observed TTP or conception delay, respectively, adjusted for maternal age, BMI, and smoking at study enrollment. The risk of prospectively observed conception delay was modeled with an indicator of any past conception delay (19), where risk ratio (RR)>1 indicates greater risk of prospective conception delay if retrospective delay was reported. Using discrete survival models with robust variances, we computed fecundability odds ratios (FOR), the odds of achieving a pregnancy in a cycle given no pregnancy in the previous cycle, for the first prospective attempt using the mean of all retrospectively-reported TTP, where FOR<1 indicates a longer TTP in the first prospective attempt for longer retrospectively-reported TTP. Analyses were conducted in SAS 9.3 (SAS Institute Inc., Cary, NC).

Results

75 women with 2 prior pregnancies contributed 180 retrospectively-reported and 91 prospectively observed TTPs to frailty models. RR and FOR models included 307 retrospectively-reported and 202 prospectively observed TTPs from 202 women. Only their first prospective attempt was included as the interest was whether retrospective reported trying times informed the very next prospectively observed trying time to mimic a preconception counseling office visit. Characteristics of these two samples were largely similar (Table 1a) with the only notable difference that 75% of women with 2 retrospectively-reported TTP experienced a prior pregnancy loss compared with 42% of women with 1 retrospectively-reported TTP.

Reported fecundity history and observed fecundity outcomes during the study were similar between groups (Table 1b). Median retrospectively-reported TTP was 2 months in both groups; conception delay preceding a prior pregnancy was reported by 20% and 23% of women with 2 and 1 retrospectively-reported TTPs, respectively. Median prospectively observed TTP was 4 cycles in both groups with conception delay in 22% and 25% of pregnancy attempts for women with 2 and 1 retrospectively-reported TTPs, respectively.

Comparing retrospectively-reported conception delay to the gold-standard of prospectively observed conception delay, sensitivity was 25% and 26% and specificity was 82% and 78% for women with 2 and 1 retrospective reported TTPs, respectively. When using retrospectively-reported conception delay as the test for prospectively observed conception delay, PPV was 33% and 28% and NPV was 75% and 76% for women with 2 and 1 retrospective reported TTPs, respectively. Differences in TTP between the first prospectively observed attempt and the mean of all retrospectively-reported TTP show prospectively observed TTP was longer for the majority of women (median=1 cycle longer)

in both groups, though shorter prospectively observed TTP was also observed in >25% of women in both groups (Figure 1).

Clustering of retrospectively-reported TTP was high in unadjusted (frailty variance=0.79, SE=0.24) and adjusted (frailty variance=0.89, SE=0.27) models (Table 2a). However, when prospectively observed TTPs were included with retrospectively-reported TTPs, clustering was lower (unadjusted frailty variance=0.32, SE=0.12, adjusted frailty variance=0.42, SE=0.14). Using bootstrap samples, 95% CI for the difference in frailty variance was 0.008 to 1.136 and -0.004 to 1.233 in unadjusted and adjusted models, indicating significant difference in clustering between unadjusted models and substantial difference in adjusted models. Results were similar when only the first prospective attempt was considered with all past attempts (frailty variance=0.48, SE=0.16). When restricting to shorter recall periods, clustering for all prospective attempts and past attempts within 3 years (frailty variance=0.81, SE=0.27) and 6 years (frailty variance=0.52, SE=0.18) was still lower than for retrospectively-reported TTPs alone. Mean retrospectively-reported TTP was not associated with TTP in the first prospectively observed attempt (FOR=1.00, 95% CI=0.99–1.01, Table 2b), nor was past conception delay associated with prospectively observed conception delay in the first attempt (RR=1.07, 95% CI=0.57–2.01, Table 2c). The above models were assessed for heterogeneity by pregnancy loss; none were statistically significant.

Discussion

To our knowledge, this is the first assessment of TTP clustering across multiple pregnancy attempts where at least one attempt has been measured by the gold-standard, prospective measurement. We find retrospectively-reported TTP clustering is high, though notably lower when incorporating prospectively observed TTP. We found past trying times, measured by TTP or conception delay, did not inform prospective trying times. Collectively, these results suggest the high clustering for retrospectively-reported TTP may reflect reliability of recalled TTP (20) but not the actual TTP. Recall period may be important as clustering is higher when retrospective report is restricted to 3 years compared with reports 6 or 10 years.

Our findings are consistent with two previous studies reporting high clustering of retrospectively-reported TTP (7, 8). They also corroborate the low clustering of prospectively observed TTP in women with pregnancy losses (9). A possible explanation for the differences in clustering may reflect the limited validity of retrospectively-reported TTP relative to the gold-standard of prospectively observed TTP; validity has been shown to be good for short (<20 months) (21) but not long term (10 years) (12) recall. Our data show that even when restricted to a recall period of \approx 6 years, within-woman clustering is low when prospectively observed TTP is considered along with retrospectively-reported TTP.

As previous work on clustering of prospectively observed TTP was conducted among women with fecundity impairment, we considered pregnancy loss status in our analysis. We did not observe differences in the extent of clustering by prior pregnancy loss; retrospectively-reported TTP is apparently not influenced by prior loss. This finding may

suggest that clustering of prospectively observed TTPs in general is low, perhaps reflecting changes in underlying couple fecundity over time, other exposures, or even change in partnerships. Due to the LIFE Study design, we only have information on multiple prospectively observed attempts for women with observed losses and cannot evaluate prospectively observed TTP clustering by loss status; however, clustering was only slightly higher when only the first prospective attempt was considered alongside retrospectively-reported TTPs.

These findings suggest past trying times as measured by self-reported TTP or its related impairment (conception delay) are not highly informative about future prospectively observed trying attempts. If corroborated, these data may reassure couples concerned about repeating prolonged trying times. Further, if TTP as measured by the gold-standard is informative for pregnancy outcomes or later adult health (22–25), efforts to enhance couple's accurate counting and report seem warranted.

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List of abbreviations

TTP	time-to-pregnancy
hCG	human chorionic gonadotropin
BMI	body mass index
RR	risk ratio
IQR	interquartile range
SE	standard error
FOR	fecundability odds ratio
PPV	positive predictive value
NPV	negative predictive value

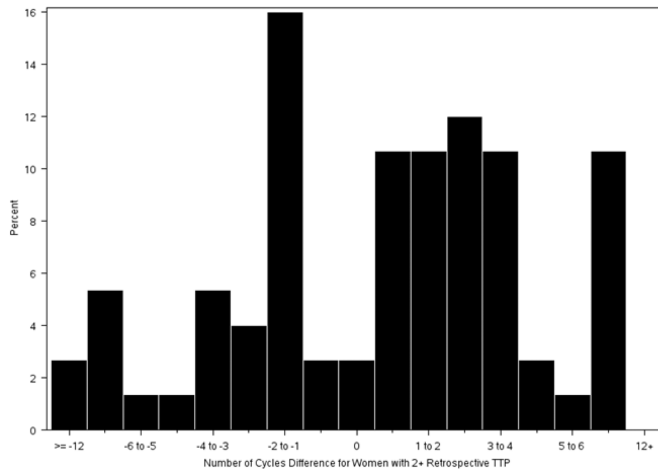
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A. Women with ≥ 2 retrospectively reported TTP
 Median: 1 cycle longer, IQR: 1.25 cycles shorter, 3.25 cycles longer



B. Women with ≥ 1 retrospectively reported TTP
 Median: 1 cycle longer, IQR: 2 cycles shorter, 3.5 cycles longer

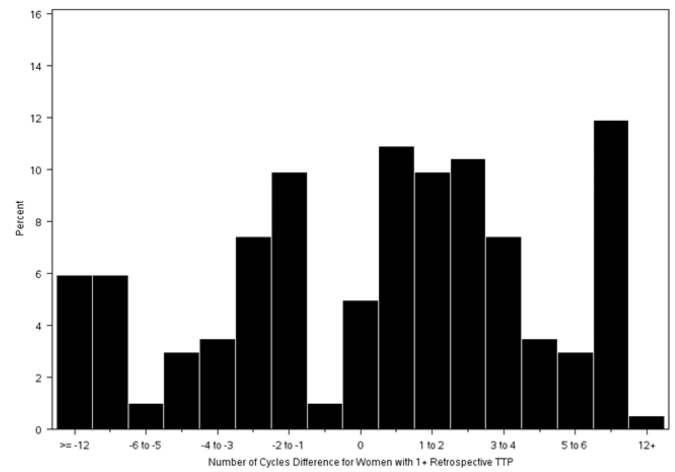


Figure 1.
 Difference in TTP between first prospectively observed attempt and mean of all retrospectively reported attempts with positive integers indicating a longer and negative integers a shorter prospectively observed TTP.

Table 1

a. Demographic Characteristics Among Women with 2 and 1 Retrospectively Reported Time-to-Pregnancies

	Women with 2 Retrospectively Reported TTP (n=75)	Women with 1 Retrospectively Reported TTP (n=202)
	Median (IQR) ^a	Median (IQR)
Age at study enrollment	33 (29, 36)	32 (29, 34)
Body mass index at study enrollment	27.2 (22.5, 31.7)	26.2 (22.7, 31.0)
	n (%)	n (%)
Smoked at study enrollment	8 (11)	19 (9)
Nulliparous at study enrollment	7 (9)	20 (10)

b. Fecundity for Retrospectively Reported and Prospectively Observed Pregnancy Attempts Among Women with 2 and 1 Retrospectively Reported Time-to-Pregnancies

	Women with 2 Retrospectively Reported TTP (n=75)	Women with 1 Retrospectively Reported TTP (n=202)
Fecundity History at Enrollment	Median (IQR)	Median (IQR)
TTP ^b for past pregnancies	2 (1, 5)	2 (1, 6)
Recall period for all past pregnancies ^c	4 (3, 6)	4 (3, 6)
Recall period for first past pregnancy	5 (4, 8)	4 (3, 6)
	n (%)	n (%)
Conception delay ^d in past pregnancy	15 (20)	47 (23)
Pregnancy loss in past pregnancy	56 (75)	85 (42)
Prospectively Observed Fecundity Outcomes	Median (IQR)	Median (IQR)
TTP in LIFE Study	4 (2, 6)	4 (2, 6)
	n (%)	n (%)
Conception delay in LIFE Study	20 (22)	50 (25)
Pregnancy loss in LIFE Study	22 (29)	49 (31)

^a Interquartile range^b Time-to-pregnancy (in months for retrospective report, in cycles for prospective observation)^c Recall period is time since pregnancy, including past year (minimum of 1 year recall)^d Conception delay is TTP > 6 cycles or months

Table 2

a. Frailty Models for Time-to-Pregnancy (TTP)

Model	Number of TTPs ^a	Frailty variance ^b	Standard error
All retrospective pregnancies, unadjusted	180	0.79	0.24
All retrospective pregnancies and prospective attempts, unadjusted	271	0.32	0.12
All retrospective pregnancies and first prospective attempt, unadjusted	255	0.38	0.14
All retrospective pregnancies, adjusted ^c	180	0.89	0.27
All retrospective pregnancies and prospective attempts, adjusted ^c	271	0.42	0.14
All retrospective pregnancies and first prospective attempt, adjusted ^c	255	0.48	0.16
All prospective attempts and retrospective pregnancies within past 3 years ^c	165	0.81	0.28
All prospective attempts and retrospective pregnancies within past 6 years ^c	238	0.52	0.18
All prospective attempts and retrospective pregnancies within past 10 years ^c	261	0.37	0.14

b. Model for Discrete TTP in First Prospective Attempt (n=202)

	Unadjusted		Adjusted ^e	
	FOR ^d	95% CI	FOR	95% CI
Mean discrete TTP in past attempts	0.99	0.98, 1.01	1.00	0.99, 1.01
Age at study enrollment	0.92	0.88, 0.96	0.92	0.88, 0.96
Body mass index at study enrollment	0.97	0.94, 1.00	0.98	0.95, 1.01
Smoker at study enrollment	0.52	0.30, 0.89	0.49	0.28, 0.86

c. Model for Conception Delay in First Prospective Attempt (n=202)

	Unadjusted		Adjusted ^e	
	RR ^f	95% CI	RR	95% CI
Conception delay in past attempt	1.16	0.62, 2.18	1.07	0.57, 2.01
Age at study enrollment	1.09	1.01, 1.17	1.08	1.00, 1.16
Body mass index at study enrollment	1.04	1.00, 1.07	1.03	1.00, 1.07
Smoker at study enrollment	1.31	0.56, 3.08	1.21	0.51, 2.85

^aNumber of TTPs included in the frailty model

^bDiscrete Cox frailty model with lognormal frailty distribution

^cAdjusted for age, BMI, and smoking status at each pregnancy attempt

^dFecundability odds ratio

^eAdjusted for all covariates listed in table

^fRisk ratio