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Brief communication

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

Katherine J. Sapra MPH [a,*], Alexander C. McLain PhD [b], José M. Maisog MD, MS [c], Rajeshwari Sundaram PhD [a], Germaine M. Buck Louis PhD, MS [a]

[a] Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Rockville, MD
[b] Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC
[c] Glotech, Inc., Rockville, MD

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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 or more retrospectively reported and 1 or more prospectively observed TTPs. We further investigated whether past trying times inform future trying time among women with 1 or more retrospectively reported and 1 or more prospectively observed TTPs.
Methods: Five hundred one couples attempting pregnancy were prospectively observed until human chorionic gonadotropin 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, body mass index, smoking at each attempt. Utility of past attempts to inform future attempts was assessed with discrete Cox models and relative risk regression, adjusted for enrollment age, body mass index, smoking.
Results: Seventy-five women with 2 or more 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 or more 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.

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Introduction

Several reproductive outcomes cluster within women, including pregnancy loss, preterm birth, pre-eclampsia, 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 United States reported high-TTP clustering [7,8]. In contrast, using data from a U.S. 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 or more retrospectively reported and 1 or more prospectively observed TTPs. We further investigated whether retrospectively reported trying times informed prospectively observed trying time for women with 1 or more retrospectively reported and 1 or more prospectively observed TTPs.

* Corresponding author. Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, 6100 Executive Blvd., Room 7B05, Rockville, MD 20852. Tel.: +1-301-435-6936; fax: +1-301-402-2084.
E-mail address: katherine.sapra@nih.gov (K.J. Sapra).

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Material and methods

Study population

The Longitudinal Investigation of Fertility and the Environment Study is a population-based, preconception cohort of 501 couples recruited on 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 or sterility. Inclusion criteria comprised couples in a committed relationship, intending to begin pregnancy attempts or off contraception for 2 months or less, partners communicate in English or Spanish, men aged 18 years or more and women aged 18 to 40 years, menstrual cycle lengths between 21 and 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 before 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 age 15 years until enrollment. 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 (Swiss Precision Diagnostics, Geneva, Switzerland, formerly Unipath). 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 human chorionic gonadotropin 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 before 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 = 27–35). Conception delay was defined as TTP more than 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 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 or more 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 (SEs) 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. Five-hundred 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 (CI) 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 or more 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 or more 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) more than 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 less than 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

Seventy-five women with 2 or more 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 1) with the only notable difference that 75% of women with 2 or more retrospectively reported