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Compliance with daily, home-based collection of urinary biospecimens in a prospective, preconception cohort

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Background: Exposures in the periconceptional environment may impact fertility and future health. Assessing time-varying exposures during the periconceptional window requires identifying approximate fertile windows around ovulation. In this prospective cohort study, we instructed women in daily cervical fluid observation and interpretation to identify incipient ovulation; they used this information to time daily urine collection for both partners. Timing and completeness of collection were compared to expert review.

Methods: One hundred seventy couples planning pregnancy enrolled from community volunteers from 2011 to 2015; women were taught the Peak Day method to identify fertile windows. Both partners collected daily urine specimens from the first day of fertile-quality fluid (estimator of the beginning of fertile window). Men discontinued on the estimated day of ovulation/conception +2 days; women continued through the onset of next menses, or positive pregnancy test at estimated day of ovulation/conception +18 days. We compared dates from samples with participants' fertility charts to determine proportion correctly collected. Also, expert reviewers judged on which days urine should have been collected, determining investigator-identified sampling days.

Results: One hundred sixty-nine couples submitted 6,118 urine samples from 284 cycles. Reviewers and participants agreed in 87% of cycles for the date of the beginning of the fertile window ±3 days (65% exact-day agreement); agreement on ovulation date, ±3 days, was 93% (75% exact-day agreement). Five thousand three hundred twenty-nine female samples were expected based on investigator-identified sampling days, and 4,546 were collected, of which 82% were correctly collected on expected days. Fifty-nine percent of male samples were correctly collected relative to investigator-identified sampling days.

Conclusions: Intensively-scheduled, biologically-triggered, at-home biospecimen collection can successfully be targeted to the periconceptional window and completed in a longitudinal cohort study.

Keywords: Peak Day method; Preconception; Fertility; Urinary biospecimens

Introduction

The periconceptional and prebirth environment has come under increasing scrutiny in recent years, with broadening understanding regarding the ways in which exposures during these periods may shape both fertility and future health and development.[1] A growing body of research is exploring relationships between various exposures and reproductive and fetal outcomes,[2–6] but this research has produced as many questions as answers.

One difficulty of early exposure research is the transient nature of many exposures of interest.[6,7] Endocrine disrupting chemicals, which have been implicated in a wide range of fertility issues and health outcomes for developing neonates, often possess biological half-lives measured in hours.[8] This fact, combined with the limited state of current understanding regarding exposure windows of importance in the periconceptional and gestational periods, makes such relationships difficult to investigate and requires specialized study designs.[2,9]

Longitudinal cohort studies, beginning preconception, hold promise regarding periconceptional exposures and birth outcomes.[2,10–12] The utility of such a design depends on sufficient exposure measurements, timed such that exposures during the narrow band of fertile time are fully assessed.[10,12] The number of measurements required can become costly for investigators and unwieldy for subjects, leading to noncompliance and loss to follow-up.[13,14] These hurdles can be offset by the use of at-home biospecimen collection protocols, in which subjects, having been trained in collection procedures and provided with sampling schedules and materials, collect specimens at home for later collection by study investigators.[13–15]

This article examines whether such a schema, used for the collection of urine from both members of pregnancy-seeking couples at carefully scheduled, participant-identified intervals

What this study adds

We believe that this article shows the ability of participants to successfully evaluate and collect biospecimens on a rigorous, biologically-determined schedule in their own homes with an acceptable degree of compliance. This proved vital to our study of the periconceptional environment, and it is extendable to many other study objectives.

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surrounding days of fertility and ovulation, can be performed with high compliance.

Methods

The results we present were collected from within an observational, prospective cohort study designed to accomplish home-collected, individual-level biomonitoring among heterosexual couples during the sensitive windows of conception, implantation, and very early pregnancy. Study procedures have previously been described, including recruitment and informed consent.[7] The study was approved by the University of Utah Institutional Review Board. Briefly, women were taught to recognize changes in cervical fluid that prospectively indicate the onset of the fertile window, and were trained to identify the estimated day of ovulation, which may be also be the estimated day of conception (EDO/C), during the menstrual cycle (based on the Peak Day method).[16] These observations were recorded on a daily fertility chart that was turned in to the study staff at the end of the cycle (see Supplemental Digital Content 1; http://links.lww.com/EE/A46). Men and women both were asked to collect daily first-morning urine samples (first void upon waking) from the first day of fertile-quality cervical fluid throughout the fertile window until the EDO/C+2 days. Men were asked to discontinue collecting after EDO/C+2 days (the end of the biologically relevant time period for conception), and women were asked to continue to collect for the remainder of the menstrual cycle until the onset of the next menses or until she had a positive home pregnancy test (QuickVue, Quidel, San Diego, California), tested at EDO/C+18 days.

Women reported the dates of the onset of the fertile window and their EDO/C to the study staff as soon as identified and this was recorded as the real-time or participant-identified EDO/C and fertile window. Daily fertility charts were later independently reviewed by two expert reviewers who objectively identified the woman's EDO/C and fertile window (investigator-identified sampling days). Premenstrual fluid occurring during the last 7 days of the cycle can often mimic cervical fluid,[16,17] so expert reviewers excluded any fertile-type cervical fluid observations in the last 7 days before menses when determining the objective EDO/C.

Dates of collected urine specimens were compared to the daily fertility charts to determine which urine specimens were correctly collected on expected days, which were missed and not collected when they were expected, and which were collected on days that were not expected (either early/before the onset of the fertile window, late/after the fertile window [men] or during the first days of following cycle [women], and other/date cannot be determined). Specimens that were missed on the first day of the fertile window were noted separately from specimens missing on other days, because first-morning specimen collection may not have been possible if the woman first noticed fertile-quality cervical fluid later in the day. Additionally, a woman's specimen that was collected on the first day of menses for the following cycle was considered expected and correctly collected for the previous cycle because she likely noticed the onset of menses later in the day after the sample was already collected. The proportions of correctly and incorrectly collected samples, according to both investigator-identified and participant-identified windows, were compared according to participant demographics and cycle to assess overall compliance.

Results

As shown in Figure, 6,246 urine samples were submitted from 286 cycles collected by 170 couples. Forty samples were excluded for inadequate labeling leaving 6,206 samples available for analysis; 4,727 collected by women and 1,479 collected by men. Among the 170 couples and 286 cycles for which we have samples, two cycles belonging to one couple are not included in participant-identified assessments because, although urine was collected and a chart was turned in, no real-time participant-identified EDO/C was reported. Additionally, 10 cycles belonging to nine couples are not included in investigator-identified assessments because an objective EDO/C could not be identified for the following reasons: (1) no fertile-fluid occurred before the last 7 days of the cycle (n = 3); (2) fertile-fluid was not correctly recorded on the chart (n = 2); or (3) the chart is missing (n = 5), reducing the final count to 274 cycles. One hundred sixty-four individuals have cycles included in both participant- and investigator-identified assessments, five individuals are not included in participant-identified but are included in investigator-identified, and five are included in investigator-identified but not included in participant-identified, for a total of 169 individuals in each stratum, noting that the couples excluded from the investigator-identified results are not the same as those excluded from the participant-identified results.

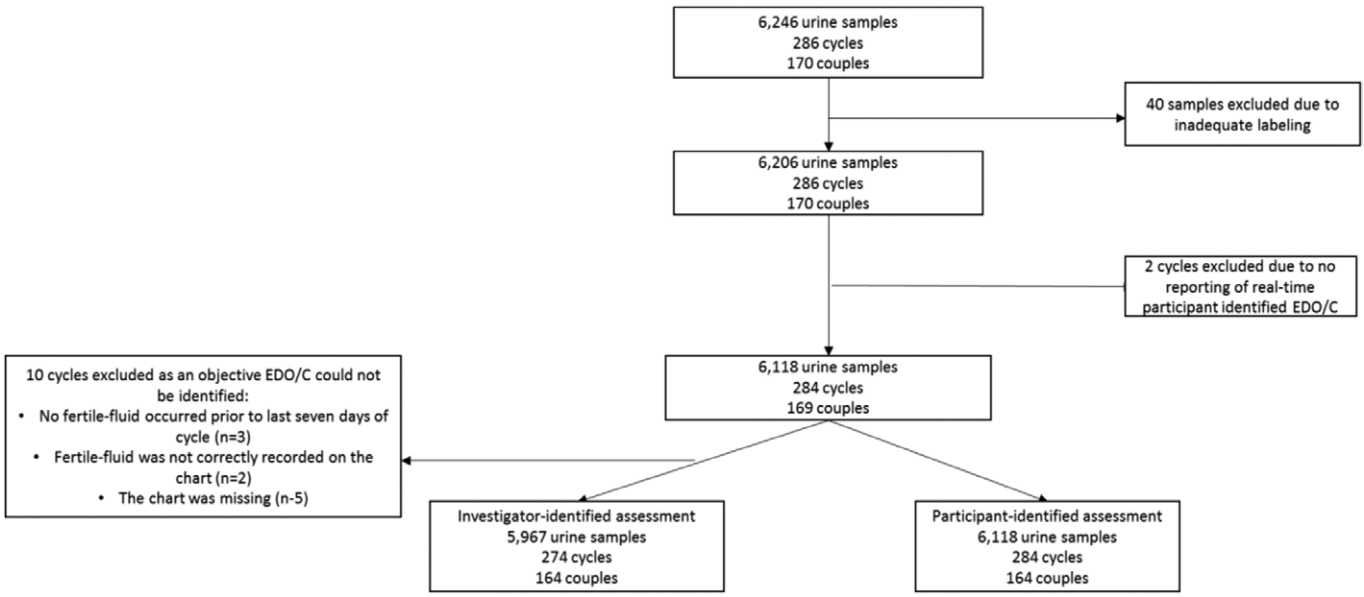

Figure. Flowchart for participant and cycle inclusion.

Table 1

Agreement between participant-identified and expert-identified EDO/C and onset of fertile window according to the Peak Day method of fertility tracking among biospecimen cycles (n = 274[a])

	EDO/C	Onset of fertile window
No. days	Cumulative no. cycles (%)	Cumulative no. cycles (%)
Exact day	204 (75)	178 (65)
±1 day	229 (84)	212 (77)
±2 days	242 (89)	231 (84)
±3 days	254 (93)	239 (87)
±4 days	260 (95)	248 (90)
±5 days	264 (96)	250 (91)
±>5 days	274 (100)	274 (100)

[a]Among 286 total specimen-collection cycles, 274 from 164 couples had an EDO/C and fertile window identified by both the woman and expert reviewer (in two cycles the woman collected specimens but did not report a real-time EDO/C and in 10 cycles the woman identified an EDO/C but reviewers could not).

As shown in Table 1, the expert reviewer and participant agreed with the exact date of the first day of the fertile window in 65% (n = 178) of cycles, and 87% for agreement ±3 days of the participant-identified date. The expert reviewer and participant agreed with the exact date of the EDO/C in 75% (n = 204) of cycles, and 93% for agreement ±3 days of the participant-identified date.

The average duration of the fertile window, as identified by the expert reviewer, was 6.9 days (SD = 4.0) and the mean was 6 days (data not shown). Nearly 17% of cycles were 3 days of length or less (2.9% 1 day, 4.0% 2 days, and 9.5% 3 days). The average participant identified fertile window was slightly shorter with an average of 5.2 days (SD = 2.3), median of 5 days, and 18.2% of cycles being 3 days of less.

Compliance among women

Using investigator-identified EDO/C dates and fertile windows (Table 2), 5,329 urine samples were expected and 4,546 were collected. Eighty-two percent of expected samples were correctly collected on expected days, 15% were not collected, and 3% of expected samples missed were to have been collected on the first day of the fertile window. A total of 5% of collected samples were collected on days that were not expected (i.e., samples collected early, late, or where dates could not be determined or appeared incorrect as written). The proportion of correctly collected samples did not vary by woman's age, and varied slightly by income level (range 77%–92%) and education level (range 81%–90%). The majority of women (n = 116) had income ranging from $20,000 to $74,999 and correctly collected 80%–82% of expected specimens. Similarly, most women were college graduates (n = 117) and correctly collected 81% of expected specimens. Compliance was similar but slightly higher when examined based on the EDO/C identified and reported by the woman in real-time (participant-identified EDO/C dates and fertile windows). Five thousand two hundred nineteen specimens were expected and 4,650 were collected, of which 85% were correctly collected on expected days. Among all categories for age, income, and education, and by both participant- and investigator-identified assessments, 0%–6% of the collected samples were collected on days that were not expected and were either early, late, or collected on days that were not consistent with cycle dates.

The proportion of correctly collected specimens was slightly (3%) less from the first cycle of collection to the second in both participant- and investigator-identified assessments (Table 3).

Compliance among men

Men correctly collected 59% (1,421 out of the 2,049 expected samples) of samples when examined using investigator-identified sampling days, and 69% (1,468 out of the 1,763 expected samples) of samples when examined using participant-identified sampling days (Table 2). There was little variability in the proportion of correctly collected specimens when stratified by education, income, and age; with proportions ≥50% in all groups by both participant-identified and investigator-identified measurement. Men missed sample collection on the first day of the woman's fertile window with proportions ranging from 9% to 12%, and frequently continued specimen collection past the EDO/C+2, with proportions of late samples ≥10% in each stratum. The proportion of correctly collected specimens was very similar in the first cycle and the second cycle, whereas the proportion of specimens collected late decreased from 15% to 9% (Table 3).

Discussion

This study, like others in a growing body of research, demonstrates that a prospective pregnancy study can successfully gather intensively scheduled urine samples from both members of the couple.[4,10,14,15,18] It further demonstrates that, in a study setting, women can be taught to understand biomarkers of ovulation and record their ovulatory cycles with a high degree of accuracy, building on past research with similar findings.[16,18,19] Additionally, we demonstrate that women can apply their observations of ovulatory signs to trigger biospecimen collection at their own biologically relevant times.

Studies seeking to examine the periconceptional environment have several options for urine collection. Women or couples can be instructed to collect urine daily, which may minimize the risk of missing important fertility windows but can be resource-intensive;[20–23] fixed calendar or menstrual cycle days can be used, simplifying collection instructions but not capturing all fertile days;[4,20] and various methods to detect the hormonal surge leading up to ovulation can be employed, allowing exposure ascertainment to begin before ovulation occurs. Hand-held electronic monitors, which track luteinizing hormone and an estradiol metabolite, are the most common method used by studies to track ovulation; these have been shown effective at restricting urine collection to the fertile window,[14,15] but may prove expensive in a large study. This study used women's observations of their cervical mucus to detect impending ovulation, a method validated against hand-held urine monitors in previous studies and which is both conservative of study resources and accurate.[16,22,24,25]

In this study, women correctly collected 82% of samples on expected days, as identified by expert reviewers (investigator-identified); men correctly collected as expected by reviewers 59% of the time. This compares well with other studies requesting daily urine collection from women and cycle-timed collection of varying length from men. Bonde et al[4] instructed women to collect daily first morning urine beginning on the first day of menstrual bleeding and continuing through day 10 for six cycles or until pregnancy, while their partners were asked to provide pre- and post-shift monthly spot urine samples (two total) during the same period; they reported a compliance rate of 84% for women and 59% for men. Ronnenberg et al[23] instructed women to collect daily urine samples for 12 months or until achieving pregnancy; they had an 82% compliance rate–equivalent to compliance observed in this study. Wilcox et al[21] asked women to collect daily first-morning urine for up to 6 months, or until becoming pregnant, when they were to collect until 8 weeks from their last menses; they reported 98% compliance and their partners were not asked to participate in urine collection. These studies instructed women to collect urine daily, without regard for cycle status and also achieved high compliance.[20,21] It is possible that this is a routine more conducive to compliance since it is unnecessary to determine each day's collection status, but it is highly resource intensive.

Table 2

Daily urine sample compliance stratified by selected demographics and participant- or investigator-identified EDO/C determination

	Investigator-identified										Participant-identified									
	n	Expected (n)	Collected (n)	Correct[a,b] (%)	Missed[a,c] (%)	Missed (first)[a,d] (%)	Early[e,f] (%)	Late[f,g] (%)	Other[f,h] (%)		n	Expected (n)	Collected (n)	Correct[a,b] (%)	Missed[a,c] (%)	Missed (first)[a,d] (%)	Early[e,f] (%)	Late[f,g] (%)	Other[f,h] (%)	
Women																				
Total	169	5,329	4,546	82	15	3	2	2	1		169	5,219	4,650	85	12	3	3	2	0	
Education																				
College (>4 years)	117	3,692	3,099	81	16	3	1	2	1		116	3,577	3,146	84	13	3	2	2	1	
College (1–3 years)	48	1,506	1,326	83	14	3	3	1	1		49	1,511	1,383	85	12	3	5	2	0	
High school	3	96	89	90	7	3	0	3	0		3	96	89	90	6	4	0	3	0	
Missing	1	35	32	86	14	0	0	6	0		1	35	32	86	14	0	0	6	0	
Annual income[i]																				
≥$100,000	14	418	343	77	20	3	2	3	1		14	403	343	79	18	3	3	3	1	
$75,000–$99,000	17	467	421	89	9	2	1	0	0		17	489	454	88	9	3	3	2	0	
$40,000–$74,999	61	1,877	1,555	80	17	3	2	1	1		61	1,827	1,570	83	14	3	2	1	1	
$20,000–$39,000	55	1,768	1,523	82	15	3	2	2	1		56	1,765	1,596	85	12	3	3	2	0	
<$20,000	18	675	590	83	15	2	4	1	0		17	610	573	88	56	15	5	1	0	
Missing	4	124	114	92	6	2	0	0	0		4	125	114	91	7	2	0	0	0	
Age (years)																				
<25	43	1,357	1,146	82	15	3	0	2	0		43	1,384	1,191	84	13	3	0	2	0	
25–29	83	2,607	2,249	82	15	3	3	1	1		83	2,455	2,266	87	12	3	4	1	0	
30–35	43	1,365	1,151	81	16	3	2	1	1		43	1,340	1,193	84	13	3	3	2	1	
Men																				
Total	169	2,049	1,421	59	32	9	2	13	0		169	1,763	1,468	69	21	10	3	14	0	
Education																				
College (>4 years)	97	1,146	841	61	30	9	2	14	0		97	1,006	875	71	20	9	3	16	0	
College (1–3 years)	63	805	503	55	35	10	2	10	1		63	672	513	65	24	11	3	10	1	
High school	8	90	69	62	29	9	0	19	0		8	77	72	71	17	12	6	18	0	
Missing	1	8	8	50	38	13	0	50	0		1	8	8	50	38	13	0	25	25	
Annual income[i]																				
≥$100,000	12	116	87	60	28	12	1	18	0		12	114	87	61	26	12	2	17	0	
$75,000–$99,000	22	241	166	60	32	8	2	11	0		22	201	169	72	17	10	2	12	0	
$40,000–$74,999	61	767	544	59	32	9	3	14	0		62	678	565	68	22	10	2	16	0	
$20,000–$39,000	48	587	394	59	31	10	2	10	1		47	486	417	72	19	10	4	12	0	
<$20,000	22	285	198	61	31	8	2	11	0		22	247	198	66	25	9	5	13	0	
Missing	4	53	32	40	49	11	0	31	0		4	37	32	59	24	16	0	22	9	
Age (years)																				
<25	21	278	167	50	40	10	3	12	2		20	208	168	69	19	12	2	12	1	
25–29	88	1,053	763	63	28	9	1	11	0		88	946	788	71	20	9	2	12	0	
30–35	55	615	399	55	36	9	3	13	0		55	523	420	65	25	10	5	14	0	
>35	9	103	92	61	26	13	2	29	0		9	86	92	69	20	12	3	33	0	

[a]Denominator for calculation of percentage is total samples expected.

[b]Correctly timed specimens includes specimens collected on the first day of the woman's menses for the following cycle given that she likely noticed the onset of menstruation after specimen collection occurred in the morning.

[c]Samples missed on any day except the first day of woman's fertile-quality cervical fluid.

[d]Samples missed on first day of woman's fertile-quality cervical fluid.

[e]Incorrectly timed. Collected before the first day of fertile-quality cervical fluid marked on fertility chart.

[f]Denominator for calculation of percentage is total samples collected.

[g]Incorrectly timed. Collected after the first day of menses for the following cycle.

[h]Samples collected where dates cannot be determined or appear incorrect as written.

[i]Combined household income. U.S. Dollars.

Table 3

Daily urine sample compliance by cycle, sex, and participant- or investigator-identified EDO/C determination

	Women								Men							
	Expected (n)	Collected (n)	Correct[a] (%)	Missed (%)	Missed (first)[b] (%)	Early[c] (%)	Late[d] (%)	Other[e] (%)	Expected (n)	Collected (n)	Correct[a] (%)	Missed (%)	Missed (first)[b] (%)	Early[c] (%)	Late[d] (%)	Other[e] (%)
Participant-identified																
First cycle	3,122	2,780	86	11	3	2	1	0	992	862	69	20	11	4	16	0
Second cycle	2,097	1,870	83	14	3	3	3	0	771	606	68	23	9	2	11	0
Investigator-identified																
First cycle	3,210	2,746	83	14	3	2	1	1	1,195	834	57	33	9	2	15	0
Second cycle	2,119	1,800	80	17	3	3	3	0	854	587	61	30	9	2	9	0

[a]Correctly timed specimens includes specimens collected on the first day of the woman's menses for the following cycle given that she likely noticed the onset of menstruation after specimen collection occurred in the morning.

[b]Samples missed on first day of woman's fertile-quality cervical fluid.

[c]Incorrectly timed. Collected prior to the first day of fertile-quality cervical fluid marked on fertility chart. Denominator for calculation of percentage is total samples collected rather than total samples expected.

[d]Incorrectly timed. Collected after the first day of menses for the following cycle. Denominator for calculation of percentage is total samples collected rather than total samples expected.

[e]Samples collected where dates cannot be determined or appear incorrect as written.

Several other studies collect spot urine samples, rather than daily samples, at time points related to the fertile window. The subjects of a study by Buck Louis et al[14] used fertility monitors to estimate ovulation and study staff collected urine twice surrounding approximate fertility time-points; their compliance ranged from 77% to 100% for women and 94% to 100% for men. Luderer et al[15] also used fertility monitors and had participating women collect a urine sample on the 10th day after the day of menses onset each month for two to three cycles; they achieved 94% compliance. These studies requesting spot urine samples demonstrate high compliance and are less resource intensive compared to studies requesting daily collection, but they may not be able to classify exposure to transient contaminants with high intrapersonal variability, such as BPA, with the same level of accuracy as studies receiving a week or more of samples.[26]

In this study, as in others, men's compliance rates were markedly lower than women's.[4,14] Further, men were more likely than women to miss the sample on the first day of the fertile window and frequently continued to collect past the EDO/C+2. It is unclear whether this is due to lack of interest or a lack of intra-couple communication regarding the onset and end of the fertile window and appropriate sampling days. Overall, future studies including male partners may wish to explicitly discuss strategies to enhance compliance and communication with enrolled couples.

Our decision to restrict sample collection to the fertile window (men) and fertile window through EDO/C+18 days (women), and to train women to detect this period through observation of their own biomarkers, yielded compliance rates comparable with studies using fertility monitors to achieve the same end.[14,15] This was a cost-effective decision for this study, compared to electronic monitors, which may cost hundreds of dollars for each monitor and at least $1 a day for test strips.[27] Additionally, the training given in the study may deepen participants' understanding of their own fertility in important, though less quantifiable, ways.[28]

Our prior validation work, and the work of others, has found that the actual date of ovulation occurs within three days of the estimated day of ovulation by the Peak Day method.[22,24,25] Theoretically, for some cycles, women could miss collecting urine on the actual day of ovulation, but this should be rare, as the average duration of the estimated fertile window with this approach was 6.9 days.

This study was limited by the relatively small size and demographic homogeneity[7] of the study population which may restrict generalizability. We recognize that couples planning pregnancy are substantially different than couples not planning pregnancy and that a high proportion of pregnancies in the United States are unplanned.[29] However, within the population of couples willing to participate in a preconception cohort, this method can achieve high compliance with cost savings from not using fertility monitoring equipment or daily sampling not relative to the fertile window.

Conclusions

This study demonstrates the possibility of achieving high levels of compliance in tightly scheduled, home urine collection in the context of a preconception pregnancy cohort. It further demonstrates the utility of subject training in biomarker identification as a method of predicting the fertile window and the periconceptional time frame. Future studies may want to consider ways to improve the communication of fertile days within couples to maximize male participation.

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