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Effects of early pregnancy loss on hormone levels in the subsequent menstrual cycle

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Abstract

Previous studies of hormone patterns after clinical miscarriage suggest reduced pituitary function. Hormonal effects of very early pregnancy loss (before six weeks gestation) have not been described. We used within-woman differences between menstrual cycles in urinary hormone measurements from women in the North Carolina Early Pregnancy Study to describe hormonal changes after very early pregnancy loss (n=28 early losses; 80 non-conception comparison cycles). We found lower pre-ovulatory luteinizing hormone and shorter luteal phase length after very early pregnancy loss, but the differences were non-significant ($p>0.3$) and smaller than those reported in the spontaneous miscarriage literature. Consistent with the reduced pituitary function reported post-spontaneous miscarriage, we found a slower rate of estrogen rise ($p=0.08$). There was no evidence of lower midluteal steroid levels as has been suggested for post-spontaneous miscarriage cycles. Very early pregnancy losses do not appear to influence subsequent menstrual cycles to the same degree as spontaneous miscarriages.

Keywords

early pregnancy loss; hormone; estrogen; luteinizing hormone

Introduction

There have been two investigations of hormone levels in the menstrual cycle after spontaneous miscarriage.[1,2] One suggested reduced pituitary function with lower follicle stimulating hormone and luteinizing hormone (LH) levels.[2] The second also suggested lower LH levels in addition to lower luteal estrogen and progesterone.[1] These hormonal changes would lead to reduced fecundability in the post-spontaneous miscarriage cycle. To our knowledge, hormone levels after very early (subclinical) pregnancy loss have not been investigated.

We explored the estrogen, progesterone, and luteinizing hormone levels in the cycle following the occurrence of a very early pregnancy loss. Our data consist of hormone

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

measures from daily first-morning urine samples. Given the variability among women in both these measures, we focused on an analysis of within-women differences.

Methods

Our data come from the North Carolina Early Pregnancy Study.[3] Briefly, the North Carolina Early Pregnancy Study (1982–1985) was a prospective cohort study designed to provide basic information on reproductive events including very early pregnancy loss [3,4], ovulation [5], and day-specific fertility [6]. Women who were planning to become pregnant were recruited from local communities and enrolled upon cessation of birth control methods. Women were excluded if they had a serious chronic illness, or if they or their partners had a history of fertility problems. Women collected first-morning urine specimens and completed daily record cards either until they became clinically pregnant or until 6 months had passed with no clinically-apparent pregnancy. Record cards included information on vaginal bleeding. All participants gave written informed consent, and the study protocol was approved by the Institutional Review Board of the National Institute of Environmental Health Sciences.

First-morning urine specimens were assayed for estrone 3-glucuronide (E_1G), pregnanediol 3-glucuronide (PdG), luteinizing hormone (LH), and human chorionic gonadotrophin (hCG). E_1G and PdG were measured by direct radioimmunoassay.[7,8] The specimens were analyzed in duplicate or triplicate and the geometric means of the daily replicates were divided by the corresponding creatinine concentration to adjust for variations in dilution. LH was measured through an immunofluorometric assay that detects both intact LH and the LH β -subunit.[9] We employed a highly-sensitive immunoradiometric assay to quantify hCG in the urine samples.[10] Pregnancy was defined as a rise in hCG that exceeded 0.025ng/ml for three consecutive days.[3] A pregnancy was categorized as an early loss if the initial rise in hCG was followed by a decline to baseline with menstrual-like bleeding beginning within 42 days of the previous menstrual period. The day of ovulation for each cycle was defined based on the rapid drop in the estrogen-to-progesterone ratio [11], using an algorithm validated by LH measurements.[12] This information combined with the participant's self-reported vaginal bleeding allowed us to define follicular phase length as the time from the first day of the last menstrual period up to, but not including, the estimated day of ovulation. [5] Luteal phase length was defined as the time from the day after ovulation up to but not including the first day of the next menstrual cycle.

We based our analyses on sets of three consecutive ovulatory menstrual cycles from a given woman ("triads"). We created two types of triads (Figure 1). One set was centered on early loss cycles that were preceded by a non-conception cycle and followed by a cycle that resulted in either a clinical conception or nonconception. The second set of triads were identical except that the middle cycle was a non-conception cycle instead of an early loss cycle. The first cycle provided a baseline for evaluating possible within-woman effects of the middle cycle on the third cycle. The proportion of third cycles that resulted in a clinical conception was similar in the two sets of triads.

We characterized the crucial aspects of hormone secretion using a set of summary variables that had been previously defined (Table 1).[13] These summary variables describe hormone secretion up through luteal day 6, prior to the occurrence of a new implantation (which usually occurs after luteal day 6).[14] Among the conceptions in the third cycle of the triads, only one implanted on luteal day 6. Our results did not change if this triad was excluded, and so it is included.

For each woman and each variable, we subtracted the hormone or phase length value in cycle 1 of the triad from the value in cycle 3, creating a baseline-adjusted summary value for each triad. We compared the baseline-adjusted values between the two types of triads and tested for statistical significance using the two-sample non-parametric Wilcoxon's rank sum test. All p-values are two-sided.

Some hormone and menstrual cycle data were missing because the participant did not provide a urine sample on a given day or because daily hormone analyses had been performed on only an a priori subset of cycles. One woman was missing information on bleeding at the start of her cycle, such that we were unable to calculate variables that depended on a specific time window in the follicular phase (mid-follicular E₁G, mid-follicular PdG, and follicular phase length).

Of the 221 participants in the North Carolina Early Pregnancy Study, 44 women had a total of 48 very early pregnancy losses. An early loss was included in the analysis if a full triad could be formed around it. We considered a cycle unobserved if the woman's first cycle in the study began after menstrual-cycle-day 6. Thirteen early losses occurred in first cycles and therefore did not have a pre-loss comparison cycle. Two losses occurred in the last cycle under observation and were also excluded. Four women had two very early losses; we included only the first in the analysis. Six triads were missing information on ovulation (but in no case was a post-loss cycle anovulatory). This left 23 early loss triads for analysis.

The comparison group of non-conception triads was assembled by selecting the earliest eligible triad of cycles in the study (women could have contributed up to six months of cycles). Women who had an early loss were not eligible to contribute a non-conception triad except for one woman who had an early loss in her last cycle in the study. Of the 178 remaining women, 91 became pregnant before providing two observed cycles and 7 were missing a known day of ovulation in the first or last cycles of the triad. This left a total of 80 non-conception triads for analysis.

Demographic characteristics were obtained from the enrollment questionnaire. Gravidity was defined as the number of pregnancies conceived before enrollment. Body mass index was calculated as weight (in kilograms) divided by height (in meters) squared and categorized according to the World Health Organization criteria.[15]

Results

Women in this analysis ranged in age from 21 to 42 with a mean of 30 (Table 2). The majority of women had at least one previous pregnancy. In both triad sets over 70% of women were of average body mass index and over 70% had never smoked. Women who provided the early-loss triads were generally similar to women who provided non-conception triads. Women in this analysis were similar overall to women in the larger study, where the mean age was 30, 65% had at least one previous pregnancy, 70% were never smokers, and 79% were of normal body mass.

In both sets of triads, the third cycle had a slower rate of estrogen rise than the first cycle, but the pattern was more pronounced in the early-loss triads ($p=0.08$) (Table 3). The pre-ovulatory LH level was also lower in the early-loss triads, however the standard error was large ($p=0.31$). Luteal phase length was slightly shorter following early loss but the p-value was large ($p=0.37$).

Discussion

Consistent with the hormone patterns after spontaneous miscarriage, which showed lower LH and shorter luteal phase length [1,2], our data suggest a lower pre-ovulatory LH and a slightly shorter luteal phase length. However, these differences were small, and confidence intervals were large. The rate of estrogen rise tended to be slower after a very early pregnancy loss which is also consistent with the reduced pituitary function reported for spontaneous miscarriages. In contrast we found no evidence of reduced luteal progesterone or estrogen, as has been reported for cycles after a spontaneous miscarriage.[1] Though our sample of very early losses was limited, we have the power to detect most of the changes previously reported for spontaneous miscarriages (Table 4). The differences between post-loss cycles and comparison cycles in our data are either smaller or in the opposite direction as those reported for spontaneous miscarriages (Table 4). Thus very early pregnancy losses may influence subsequent menstrual cycles, but apparently not to the same degree as spontaneous miscarriages.

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References

1. Donnet ML, Howie PW, Marnie M, Cooper W, Lewis M. Return of ovarian function following spontaneous abortion. *Clin Endocrinol (Oxf)* 1990;33:13–20. [PubMed: 2401092]
2. Elkas JC, Cunningham DS. Effect of 1st-trimester loss on restoration of the hypothalamic-pituitary-ovarian axis. *Gynecol Obstet Invest* 1995;40:257–260. [PubMed: 8586308]
3. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, Armstrong EG, Nisula BC. Incidence of early loss of pregnancy. *N Engl J Med* 1988;319:189–194. [PubMed: 3393170]
4. Wilcox AJ, Weinberg CR, Baird DD. Risk factors for early pregnancy loss. *Epidemiology* 1990;1:382–385. [PubMed: 2078614]
5. Jukic AM, Weinberg CR, Baird DD, Wilcox AJ. Lifestyle and reproductive factors associated with follicular phase length. *J Womens Health (Larchmt)* 2007;16:1340–1347. [PubMed: 18001191]
6. Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation. Effects on the probability of conception, survival of the pregnancy, and sex of the baby. *N Engl J Med* 1995;333:1517–1521. [PubMed: 7477165]
7. Samarajeewa P, Cooley G, Kellie AE. The radioimmunoassay of pregnanediol-3 alpha-glucuronide. *J Steroid Biochem* 1979;11:1165–1171. [PubMed: 502558]
8. Wright K, Collins DC, Musey PI, Preedy JR. Direct radioimmunoassay of specific urinary estrogen glucosiduronates in normal men and nonpregnant women. *Steroids* 1978;31:407–426. [PubMed: 208199]
9. Kesner JS, Knecht EA, Krieg EF. Time-resolved immunofluorometric assays for urinary luteinizing hormone and follicle stimulating hormone. *Analytica Chimica Acta* 1994;285:13–22.
10. Canfield RE, O'Connor JF, Birken S, Krichevsky A, Wilcox AJ. Development of an assay for a biomarker of pregnancy and early fetal loss. *Environ Health Perspect* 1987;74:57–66. [PubMed: 3319556]
11. Baird DD, Weinberg CR, Wilcox AJ, McConaughy DR, Musey PI. Using the ratio of urinary oestrogen and progesterone metabolites to estimate day of ovulation. *Stat Med* 1991;10:255–266. [PubMed: 2052803]
12. Baird DD, McConaughy DR, Weinberg CR, Musey PI, Collins DC, Kesner JS, Knecht EA, Wilcox AJ. Application of a method for estimating day of ovulation using urinary estrogen and progesterone metabolites. *Epidemiology* 1995;6:547–550. [PubMed: 8562634]

13. Baird DD, Weinberg CR, Zhou H, Kamel F, McConnaughey DR, Kesner JS, Wilcox AJ. Preimplantation urinary hormone profiles and the probability of conception in healthy women. *Fertil Steril* 1999;71:40–49. [PubMed: 9935114]
14. Wilcox AJ, Baird DD, Weinberg CR. Time of implantation of the conceptus and loss of pregnancy. *N Engl J Med* 1999;340:1796–1799. [PubMed: 10362823]
15. Report of the world health organization consultation of obesity. Geneva: World Health Organization; 1997. WHO: Preventing and managing the global epidemic of obesity.

Figure 1.

Depiction of the analytic design used to assess the influence of early pregnancy loss on the subsequent menstrual cycle. Two types of triads were created and within-woman baseline adjusted measures were obtained by subtracting the value of a summary variable in cycle 1 from the value in cycle 3. Average differences were then compared across triads.

Table 1

Definitions of summary urinary hormone variables

Summary variable	Definition	Mean level in the first cycle of all the triads
Estrone-3-glucuronide (E ₁ G) (ng/mg creatinine)		
Mid-follicular E ₁ G	Geometric mean of E ₁ G for the interval starting on day 5 of the cycle and ending 3 days before luteal day 0 (the estimated day of ovulation)	27.1
Peak E ₁ G	Geometric mean of E ₁ G for 3 days, centered on the highest mid-cycle E ₁ G (the highest E ₁ G concentration in a 16-day window ending on luteal day 3)	61.7
Rate of E ₁ G rise	Slope of 3 days of E ₁ G, ending on the day before the highest mid-cycle concentration	10.0 (per day)
Early luteal E ₁ G	Geometric mean of E ₁ G for luteal days 1–4	37.4
Mid-luteal E ₁ G	Geometric mean of E ₁ G for luteal days 5 and 6	37.5
Pregnanediol-3-glucuronide (PdG) (ug/mg creatinine)		
Mid-follicular PdG	Geometric mean of PdG for the interval starting on day 5 of the cycle and ending 3 days before luteal day 0	0.61
Early luteal PdG rise	Slope of PdG for luteal days 1–5	0.76 (per day)
Mid-luteal PdG	Geometric mean of PdG for luteal day 5 and 6	4.3
Luteinizing hormone (mIU/mg creatinine)		
Pre-ovulatory	Geometric mean of LH for 3 days ending on luteal day 0.	13.7

Table 2

Demographic and physical characteristics of the women in each triad set from the North Carolina Early Pregnancy Study (1986–88).

	Early loss triads N (%) (N=23)	Non-conception triads N (%) (N=80)
Age		
20–24	1 (4)	7 (9)
25–29	12 (52)	34 (43)
30–34	8 (35)	30 (38)
≥35	2 (9)	9 (11)
Gravidity		
0	6 (27)	27 (34)
1	10 (45)	29 (36)
2	5 (23)	15 (19)
≥3	1 (5)	9 (11)
Missing	1	0
Body Mass Index		
Underweight (18.5)	2 (9)	7 (9)
Average (18.5 – <25)	18 (78)	61 (76)
Overweight (25 – <30)	2 (9)	8 (10)
Obese (≥30)	1 (4)	4 (5)
Smoker		
Current	2 (9)	8 (10)
Former	4 (17)	15 (19)
Never	17 (74)	57 (71)

Table 3

Comparison of cycle characteristics for early loss and non-conception triads.

Summary Variable	Early-loss triads		Non-conception triads		P value ^b
	N	Mean difference ^a (SE)	N	Mean difference ^a (SE)	
Estrone-3-glucuronide (E ₁ G) (ng/mg creatinine)	23		80		
Mid-follicular E ₁ G	19	0.56 (3.0)	59	-0.56 (1.3)	0.85
Peak E ₁ G	19	0.86 (6.2)	65	-1.27 (2.6)	0.93
Rate of E ₁ G rise (per day)	18	-3.2 (1.8)	63	-0.56 (1.2)	0.08
Early luteal E ₁ G	20	2.5 (1.9)	64	-1.4 (1.7)	0.36
Mid-luteal E ₁ G	18	-0.16 (2.8)	63	-1.7 (2.3)	0.83
Pregnanediol-3-glucuronide (PdG) (ug/mg creatinine)					
Mid-follicular PdG	19	0.02 (0.08)	59	-0.02 (0.03)	0.47
Early luteal PdG rise (per day)	21	0.06 (0.09)	70	-0.001 (0.07)	0.78
Mid-luteal PdG	18	0.39 (0.33)	63	0.10 (0.24)	0.28
Luteinizing Hormone (LH) (mIU/mg creatinine)					
Pre-ovulatory LH	17	-5.9 (4.7)	65	0.92 (1.3)	0.31
Follicular phase length (days)	22	1.2 (0.78)	80	1.4 (0.77)	0.56
Luteal phase length (days) ^c	16	-0.56 (0.39)	60	-0.17 (0.26)	0.37

^aThe cycle 1 value was subtracted from the cycle 3 value for each woman, for example, for women with early loss triads it is post-loss cycle value □ pre-loss cycle value.

^bTwo-sided, derived from Wilcoxon's rank sum test for difference between triads

^cOnly calculated for triads with a non-conception cycle as the third cycle.

Table 4

Comparison of the findings from the spontaneous miscarriage literature with the findings from the current analysis of the Early Pregnancy Study.

	Post-spontaneous miscarriage decrease	Decrease reported in this study	Minimum detectable difference ^a
Pre-ovulatory LH (mIU/mg)	~18 ^b	7	14
Luteal phase length (days)	1.5 ^c	0.4	1.5
Rate of estrogen rise (ng/mg/day)	Not previously examined	3	6
Luteal estrogen (ng/mg)	5 ^{d,e}	Post-loss was higher than comparison group	10.2
Luteal progesterone (ug/mg)	~1.5 ^{c,d}	Post-loss was higher than comparison group	1.2

^aBased on a two-tailed t-test and our observed standard errors, alpha=0.05. Power is 80% for all variables except luteal phase length, which was 89%.

^bIn one study, a pituitary agonist was administered after spontaneous miscarriage and six LH measures were obtained within two hours of stimulation.[2] Differences between control and post-spontaneous miscarriage women increased over time from 5.5 to 35.7 mIU/ml with all but one greater than 17. The other study reported a difference of 18.3 mIU/mg.[1]

^cFrom Donnet et al. [1]

^dThese differences were measured in the late luteal phase, while our measures are from the midluteal phase. We did not include any hormonal measures from the late luteal phase as some of the women in our study conceived, and these measures would be influenced by conception. Smaller differences in estrogen and progesterone were reported for the midluteal phase, but they were not statistically significant.[1]

^eAn exact difference was not reported, this is an approximation based on their Figure 1.[1]