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Time-varying effects of signs and symptoms on pregnancy loss <20 weeks: Findings from a preconception prospective cohort study

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Abstract

Background—Although pregnancy loss affects one-third of pregnancies, the associated signs/symptoms have not been fully described. Given the dynamic nature of maternal physiologic adaptation to early pregnancy, we posited the relationships between signs/symptoms and subsequent loss would vary weekly.

Methods—In a preconception cohort with daily follow-up, pregnancies were ascertained by self-administered sensitive home pregnancy tests on day of expected menses. We evaluated the effects of weekly time-varying signs/symptoms (including vaginal bleeding, lower abdominal cramping, and nausea and/or vomiting) on pregnancy loss <20 weeks in Cox proportional hazards models and calculated the week-specific probability of loss by presence/absence of each sign/symptom.

Results—Of 341 pregnancies ascertained by home pregnancy test, 95 (28%) ended in loss. Relationships between signs/symptoms and loss varied across time since first positive pregnancy test. In the first week following pregnancy confirmation, when many losses occurred, bleeding (hazard ratio (HR) 8.7, 95% confidence interval (CI) 4.7, 16.0) and cramping (HR 1.8, 95% CI 1.2, 2.7) were associated with loss even when accompanied by nausea and/or vomiting (HR 5.2, 95% CI 2.6, 10.5). After the second week, new relationships emerged with nausea and/or vomiting

inversely associated (HR range 0.6 to 0.3, all 95% CI upper bounds <1.00) and bleeding no longer associated with loss. Probabilities of loss of ranged from 78% (95% CI 59%, 96%) with bleeding present in week 1 to 8% (95% CI 5%, 12%) with nausea/vomiting present in week 5.

Conclusions—Relationships between signs/symptoms and pregnancy loss vary in early pregnancy possibly reflecting maternal physiologic response.

Keywords

Bleeding; Cramping; Miscarriage; Nausea; Pregnancy loss; Symptoms; Time-varying effects; Vomiting

INTRODUCTION

Pregnancy loss affects an estimated one-third of pregnancies,^{1,2} potentially causing severe psychological trauma to women and their partners.^{3–5} Despite the frequency and consequences of pregnancy loss, its signs and symptoms during early gestation have yet to be fully described. Doing so requires preconception studies by which the earliest losses, which constitute the majority,^{1,2} can be captured and the preceding signs and symptoms prospectively ascertained.

Few preconception studies^{2,6–8} have reported the relationships between signs and symptoms and pregnancy loss. Vaginal bleeding has been associated with loss^{7,9} while nausea and/or vomiting has been inversely associated with loss.^{6–8,10} However, all previous analyses have employed fixed effect covariate modelling to estimate these associations, which assumes the relationships between signs and symptoms and loss are constant across early pregnancy.

However, given rapid maternal physiologic adaptations to early pregnancy, it is likely that the relationships between signs and symptoms and pregnancy loss may vary weekly. Therefore, we estimated the weekly associations between signs and symptoms and pregnancy loss <20 weeks gestation using time-varying effects to determine whether these relationships change across time since first positive pregnancy test.

METHODS

Study population

We used data from the Longitudinal Investigation of Fertility and the Environment (LIFE) Study, a population-based preconception cohort of 501 couples residing in 16 counties in Michigan and Texas, USA, 2005–2009, described in detail elsewhere.¹¹ Briefly, couples discontinuing contraception or off contraception 2 months in order to attempt pregnancy were screened for eligibility. Eligibility criteria included being in a committed relationship, both partners communicated in English or Spanish, men were aged 18-years-old, women were aged 18–40 years-old, had menstrual cycle lengths of 21–42 days, and had not used injectable contraception within the past year. Couples in which one or both partners had physician-diagnosed infertility/sterility were ineligible. Enrolled couples were followed until live birth or pregnancy loss, or for 12 months of unsuccessful pregnancy attempts.

Institutional Review Board approval was obtained from all sites and all participants provided written informed consent.

Study measures

Maternal baseline characteristics—At enrollment, women were interviewed to ascertain sociodemographic, lifestyle, and reproductive health information including age, race/ethnicity, education, household income, employment status, smoking status, and previous pregnancies and pregnancy outcomes. Body mass index (BMI) was calculated from height and weight measured by study personnel using standardised protocols.¹²

Ascertainment of pregnancy—At enrollment, women were provided with the ClearBlue digital urine-based home pregnancy test kit (Inverness Medical Innovations, Waltham, MA) and multiple pregnancy test sticks for each cycle. Women were instructed to test on the day of expected menses. If the test was positive, they were instructed to test again one week after the first positive pregnancy test. If the pregnancy test on the day of expected menses was negative, women were instructed to test again in one week, consistent with manufacturer's guidance. The pregnancy test had an advertised hCG sensitivity of 25 IU/L, though independent testing showed it can detect lower concentrations of pure and hyperglycosylated hCG, the predominant forms of hCG in early pregnancy.¹³ The digital readout categorised the result into 'pregnant' or 'not pregnant' and removed subjectivity in interpreting the result. Women recorded pregnancy test results in daily journals while trying for pregnancy. A single positive pregnancy test denoted hCG pregnancy.

Ascertainment of signs and symptoms—For five weeks following the first positive home pregnancy test, women recorded daily the occurrence of vaginal bleeding and its severity (none, spotting, light, moderate, heavy) using standardised pictographs.¹⁴ Women also recorded daily lower belly cramping (yes/no) and nausea and/or vomiting (none, nausea only, vomiting only, or both nausea and vomiting). This data collection corresponds to the period of embryo organogenesis, which is a dynamic time for the mother-embryo dyad.

Ascertainment of pregnancy loss—Pregnancy loss was ascertained by conversion of a positive pregnancy test to a negative pregnancy test, clinical confirmation of pregnancy loss, or onset of vaginal bleeding of an intensity and pattern consistent with expulsion of the products of conception.¹⁵ Pregnancy loss was defined as a pregnancy loss at <20 weeks gestation, exclusive of ectopic pregnancy, in keeping with the Centers for Disease Control and Prevention's definition of stillbirth as occurring at ≥20 weeks gestation.¹⁶

Statistical analysis

Time-to-event—Time-to-event, *i.e.*, pregnancy loss, was measured in days following a positive pregnancy test. Losses occurring prior to day 35 (5 weeks) following a positive pregnancy test were coded as events on the observed day. Pregnancy losses occurring ≥35 days post positive pregnancy test were coded as events on day 35 and live births and losses to follow-up ≥35 days post positive pregnancy test were censored at day 35 to facilitate the time-varying effect analyses. Once an event or censoring occurred, those observations were

removed from the denominator from all subsequent analyses (*i.e.*, a loss in week 2 would be removed from analyses for week 3 consistent with a lifetable approach).

As we were interested in assessing the time-varying effects of signs and symptoms, which were recorded only after the positive pregnancy test, on pregnancy loss, the survival time scale needed to be consistent with the time-varying effects scale (*i.e.*, time post positive pregnancy test). Additionally, the units of survival time needed to be at least as granular as the units for time-varying effects (*i.e.*, weekly or daily). Therefore, days post positive pregnancy test was chosen as the time-to-event scale.

Time-varying covariates—The values for signs and symptoms varied for each of the five weeks following a positive pregnancy test. Individual signs and symptoms for each week were coded as any versus no bleeding, light/moderate/heavy bleeding versus none/spotting only, moderate/heavy bleeding versus none/spotting/light bleeding, any versus no cramping, any versus no nausea or vomiting, any vomiting versus no nausea or vomiting, nausea only versus no nausea or vomiting. If a symptom was recorded on at least one day during the week, regardless of whether the symptom was a new occurrence or had occurred in a previous week, a woman was coded as positive for that symptom in that week. Combinations of signs and symptoms co-occurring in the same week were also constructed. All combinations were explored and the five combinations with sufficient numbers for stable estimates (5% of imputations, described below) were 1) nausea and/or vomiting, cramping, and bleeding, 2) nausea and/or vomiting and cramping, 3) nausea and/or vomiting alone, 4) cramping alone, and 5) no nausea and/or vomiting, cramping, or bleeding. The severity of bleeding included in the combinations was in two forms: any bleeding or light/moderate/heavy bleeding. All information up to and including the day prior to loss ascertainment were included in the analyses; any signs and symptoms recorded the day of or after the day of loss were not included in analyses.

Multiple imputation of signs and symptoms—We explored the data for completeness. Despite the intensity of daily collection, the signs and symptoms data were mostly complete. Among women with an ongoing pregnancy at the beginning of the week, at least one day of bleeding information (yes/no) was recorded for over 85% of women during the first 4 weeks following a positive pregnancy test and half of the women in week 5. At least one day of cramping and nausea/vomiting information (yes/no) was completed for one-quarter of women in week 1, rising to over 80% of women in weeks 2–4 and half of the women in week 5. Days with missing data were imputed using the multiple imputation ‘mice’ package in R software,¹⁷ and 100 imputed data sets were generated. For each sign or symptom, all available data were used for the imputation, including maternal characteristics, other days of information on the sign or symptom, and other signs or symptoms. Any imputed data occurring on or after the day of pregnancy loss or loss to follow-up were set to missing for the analyses.

Modelling with time-varying effects and cumulative probability of pregnancy loss—The censoring variable was recoded as binary: event if the outcome was a loss, censored if the outcome was a live birth or loss to follow-up (non-loss). The relative hazards of pregnancy loss were estimated for presence versus absence of time-varying signs and

symptoms using Cox proportional hazards models with time-varying effects. The effects of signs and symptoms on relative hazards of pregnancy loss were allowed to vary over time. A beta coefficient was estimated for each of the five weeks post pregnancy test using weekly time-varying covariates described above. The cumulative probability and 95% confidence interval (CI) of pregnancy loss by the presence and absence of individual and combinations of signs and symptoms during each week following a positive pregnancy test was estimated from Cox proportional hazards models. The above analyses were carried out on each of the 100 imputed data sets with the final results obtained by combining the results of individual data sets using Rubin's rules (PROC MIANALYZE in SAS version 9.4) to provide accurate estimates for standard errors and resulting 95% CI. We examined all maternal characteristics for evidence of confounding, *i.e.*, maternal characteristics associated with signs or symptoms and associated with pregnancy loss. None of the characteristics met these criteria and, therefore, all final models excluded maternal characteristics.

RESULTS

Characteristics of analytic cohort

Of 501 couples, 347 achieved an hCG pregnancy. Three couples had twin pregnancies and were excluded. One pregnancy loss 20 weeks' gestation and two ectopic pregnancies occurred and were also excluded leaving 341 pregnancies. Ninety-five (28%) pregnancies ended in a loss <20 weeks' gestation, 203 (60%) in a live birth, 24 (7%) in a loss to follow-up before 20 weeks, and 19 (6%) in a loss to follow-up 20 weeks' gestation. The majority of women were aged 25–34 years, non-Hispanic white, obese or overweight, non-smokers, employed, had some college education, an annual household income \$50,000, and had previously been pregnant and delivered (Table 1). The median cycle day for a positive test was day 29 (5th percentile: 23, 25th percentile: 27, 75th percentile: 32, 95th percentile: 43 days).

Weekly frequencies of signs and symptoms

Five pregnancy losses and one loss to follow-up occurred the day after the positive pregnancy test and did not contribute any information to the analysis. At the beginning of week 1 post positive pregnancy test, 335 pregnancies were ongoing, 300 were ongoing at week 2, 288 at week 3, 283 at week 4, and 271 at week 5. Overall, prevalence of any bleeding was fairly stable between weeks 1–5 (range 16–22%); however, moderate/heavy bleeding became less common as more time since pregnancy discovery passed, declining from 10% in week 1 to 1% in week 5 (Table 2). While any nausea and/or vomiting was also fairly stable (range 64–81%) prevalence of vomiting increased from week 1 to week 5 (19% to 32%). Prevalence of lower abdominal cramping decreased from week 1 to week 5 (72% to 53%). The prevalence of signs and symptoms differed by loss status (Figure 1).

Cumulative probability of pregnancy loss

Cumulative probability of pregnancy loss, which can be interpreted as risk of pregnancy loss, in the presence and absence of signs and symptoms each week are presented in Table 3. The risk of pregnancy loss in the presence (64% to 13%) and absence (20% to 11%) of bleeding decreased from week 1 to week 5 as did the risk of pregnancy loss in the presence

of vomiting (39% to 6%) or nausea (29% to 10%); in contrast, in the absence of either nausea or vomiting the risk of loss increased from week 1 to week 4 (20% to 33%). The cumulative probability of pregnancy loss by co-occurrence of signs and symptoms each week is presented in Table 4. The risk of pregnancy loss in the absence of any signs or symptoms was fairly stable across weeks 1 to 4 (24% to 30%) as was the risk of loss in the presence of cramping only (15% to 16%). The risk of pregnancy loss decreased from weeks 1 to 5 in the presence of nausea and/or vomiting either alone (18% to 11%), co-occurring with cramping (22% to 5%), or co-occurring with cramping and bleeding (71% to 6%).

Regression modelling results

Results from regression models for individual signs and symptoms are presented in Table 3. Any bleeding was associated with pregnancy loss in week 1 (hazard ratio (HR) 6.2, 95% CI 3.8, 10.2) and week 2 (HR 2.3, 95% CI 1.2, 4.3), but not in weeks 3–5. Similar results were observed for light/moderate/heavy bleeding and moderate/heavy bleeding. Any nausea and/or vomiting was not associated with pregnancy loss in week 1; however, it was inversely associated with loss in weeks 2–5 (HR range 0.6 to 0.3, all upper limits of the 95% CI were below 1.0). Similar results were observed for nausea only and any vomiting. Cramping was positively associated with pregnancy loss in week 1 (HR 1.8, 95% CI 1.2, 2.7) and inversely associated with loss in weeks 3 to 5. Results from regression models for co-occurrence of signs and symptoms are presented in Table 4. Women with all three symptoms had higher rates of pregnancy loss (HR 5.2, 95% CI 2.6, 10.5) compared with women without any symptoms in week 1 but not in subsequent weeks. In weeks 2–5, nausea and/or vomiting either alone or in combination with cramping were inversely associated with loss.

COMMENT

Main findings

In this preconception cohort, we observed substantial weekly variation in the prevalence of signs and symptoms in early pregnancy. In particular, the first week following a positive pregnancy test, when one-third of losses occurred, was different from subsequent weeks and the variability appeared to be most marked for the more severe signs and symptoms. Specifically, moderate/heavy bleeding prevalence declined from 10% in the first week to 1% in the fifth week following a positive pregnancy test, while prevalence of vomiting increased from 19% in the first week to 32% in the fifth week. The relationships between signs and symptoms and pregnancy loss also varied across time since first positive pregnancy test with symptomatology of the first week, when many losses occurred, distinct from subsequent weeks. During this time, a positive relationship between lower abdominal cramping and pregnancy loss was observed, and the positive relationship between bleeding and pregnancy loss was most pronounced. Conversely, nausea and/or vomiting were not associated with pregnancy loss in the first week but were inversely associated with loss in subsequent weeks. Additionally, the presence of all three symptoms was associated with loss in the first week but not in later weeks. Thus, the symptomatic presentation of losses in the first week following a positive pregnancy test appears different from that occurring in subsequent weeks of pregnancy.

Limitations of the data

These findings need to be interpreted considering the study's limitations. Firstly, by design daily information on signs and symptoms was collected only through the first five weeks following a positive pregnancy test; therefore, we were unable to evaluate the weekly time-varying effects of signs and symptoms on loss beyond that period. As this corresponds with the end of organogenesis and the beginning of the fetal period, associations between signs and symptoms and pregnancy loss at later gestational ages may differ from the associations documented in the early pregnancy period. Secondly, despite being the largest prospective preconception study with daily follow-up to date,¹⁸ there were few pregnancy losses beyond the first trimester. Thirdly, we were unable to examine all possible combinations of signs and symptoms owing to small numbers of women with uncommon symptomatology. Fourth, 7% of pregnancies were lost to follow-up <20 weeks' gestation, though we used a survival analysis censoring approach to account for these losses. Finally, there was some variation in cycle day of positive pregnancy test, though 49% of women tested between day 28 and 34. As the incidence of signs and symptoms and pregnancy loss changes across gestation, effect modification of the observed relationships by cycle day of test is possible.

Strengths of the study

This study also had several strengths. Firstly, the preconception design facilitated the prospective capture of signs and symptoms relative to pregnancy loss ascertainment. This minimised the potential recall bias that could arise if signs and symptoms had been elicited after the loss (*i.e.*, exposure misclassification differential by outcome). Secondly, by capturing signs and symptoms daily, we were able to evaluate these factors as time-varying covariates with time-varying effects on pregnancy loss. Thirdly, by ascertaining pregnancies using sensitive home pregnancy tests, pregnancies and pregnancy losses were captured early in gestation. This extended the relationship between signs and symptoms and pregnancy loss to very early pregnancy and thus increased the applicability of the results to contemporary cohorts of pregnant women who have information from early pregnancy testing. It also facilitated the evaluation the time-varying relationships between signs and symptoms of pregnancy loss during the period prior to onset of clinical care. Of note, the incidence of pregnancy loss in this preconception cohort (28%) is comparable to estimates from prior preconception cohort studies (26–31%).^{19–21}

Choice of time scale

Many women discover both their pregnancy and losses at home prior to clinical care entry, which makes the time scale of time post-positive pregnancy test meaningful for them, though this choice may make clinical interpretability more challenging. Additionally, when using the typical time scale of LMP-based gestational age, the time origin is taken as the LMP and the woman is considered at risk for an adverse outcome from start of LMP with zero-risk for adverse events earlier on (*i.e.*, before pregnancy discovery) leading to issues of immortal time. With the choice of positive pregnancy date as the start time, we have equated the time scales for the observation of signs and symptoms with time to loss. As the signs and symptoms are prospectively observed post-positive pregnancy test, information prior to that is subject to recall bias and would typically require assumptions on how the symptoms were

prior to recognition of pregnancy by the woman. Finally, no significant associations between main risk factors like age and time to positive pregnancy test were observed. Consequently, the unobserved time is non-informative to time to loss.

Interpretation of the findings

Time-varying effects analyses revealed some new relationships between signs and symptoms and pregnancy loss and confirmed findings previously reported from fixed effect covariate analyses. The finding that vaginal bleeding was associated with loss was consistent with reports from fixed effect covariate analyses of preconception cohorts,⁹ including fixed effect covariate analysis on this same cohort.⁷ However, we observed an association only in the first two weeks following a positive pregnancy test, which was consistent with findings from previous studies^{22,23} describing the greatest probability of miscarriage in the earliest weeks for pregnancies complicated by bleeding. Our observation that vomiting was inversely associated with loss also corroborated findings from fixed effect covariate analyses in prior preconception studies,⁸ including fixed effect covariate analysis on this same cohort,⁷ though this relationship was restricted to later weeks. Similarly, we found that isolated nausea was inversely associated with loss after the first week, which corroborated reports from one previous analysis⁸ and contrasted fixed effect covariate analysis on this same cohort where no association was observed.⁷ The observation that lower abdominal cramping was positively associated with loss in the first week following a positive pregnancy test and inversely associated with loss in later weeks contrasted with results from fixed effect covariate analysis on this same cohort where no association was observed overall.⁷ Our study corroborated results from previous fixed effect covariate analyses on this cohort regarding the occurrence of multiple signs and symptoms:⁷ cramping with nausea and/or vomiting was inversely associated with loss, though only after the first week, while cramping with bleeding and nausea and/or vomiting was positively associated with loss only during the first week. Overall, time-varying effects analyses revealed that the associations between signs and symptoms and pregnancy loss vary across time since first positive pregnancy test and that fixed effect covariate analyses obfuscate the marked changes in symptomatology associated with losses in the earliest weeks of pregnancy discovery.

With these time-varying effect analyses, we build upon our previous work on the same cohort using fixed effect covariate analyses,⁷ uncovering more nuanced relationships between signs and symptoms and loss. We previously found vaginal bleeding was associated with loss; in this study, vaginal bleeding is only associated with loss in the first two weeks post-positive pregnancy test. Similarly, we previously found vomiting was inversely associated with loss; in this study, vomiting is only inversely associated with loss after the first two weeks post-positive pregnancy test. And while we previously found no association between lower abdominal cramping and loss, in this study, cramping is associated with loss, but only in the first week post-positive pregnancy test.

Conclusions and implications

Our preconception cohort study showed that there is a dynamic relationship between signs and symptoms and pregnancy loss across time since pregnancy discovery. In the first week

following a positive pregnancy test, when many losses occur, bleeding and cramping are associated with loss even if accompanied by nausea and/or vomiting. However, new relationships between signs and symptoms emerge after the second week, with nausea and/or vomiting inversely associated and bleeding no longer associated with pregnancy loss. Symptomatic presentation of pregnancy loss varies by week since pregnancy discovery, and this has clinical implications if corroborated in future preconception studies. While these results suggest that vaginal bleeding in the first two weeks after the first positive pregnancy test is associated with a higher rate of pregnancy loss and that nausea and/or vomiting is indicative of a positive pregnancy prognosis in later weeks, the maternal physiologic responses to early pregnancy, causes of signs and symptoms and their relation to pregnancy loss require more basic science, clinical, and epidemiologic research. Developing prognostic models for pregnancy loss based on time-varying signs and symptoms will be useful for women and clinicians in terms of understanding the physiologic and pathologic processes associated with early pregnancy and pregnancy loss.

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Figure 1.

Weekly Prevalence of Signs and Symptoms by Pregnancy Loss Status Among Women in the LIFE Study, Michigan and Texas, USA, 2005–2009

Table 1

Baseline Characteristics of Women with Singleton Pregnancies in the LIFE Study, Michigan and Texas, USA, 2005–2009

	n (%) ^a
Age (years)	
18–24	25 (7)
25–29	158 (46)
30–34	114 (33)
35–40	44 (13)
Race/Ethnicity	
Non-Hispanic White	283 (84)
Non-Hispanic Black	6 (2)
Hispanic	29 (9)
Other	20 (6)
Education	
High school or less	15 (4)
Some college or more	322 (96)
Income (US dollars)	
<\$50,000	44 (13)
\$50,000–99,999	161 (48)
\$100,000+	127 (38)
Employed	
No	68 (20)
Yes	273 (80)
Prepregnancy body mass index (kg/m ²)	
<18.5	5 (1)
18.5–24.9	164 (48)
25.0–29.9	88 (26)
30.0	83 (24)
Site	
Michigan	65 (19)
Texas	276 (81)
1 Prior pregnancy	
No prior pregnancy	132 (39)
Prior pregnancy	209 (61)
1 Prior delivery (among those with 1 prior pregnancy)	
No prior delivery	27 (13)
Prior delivery	179 (87)
1 Prior loss (among those with 1 prior pregnancy)	
No prior loss	139 (67)
Prior loss	68 (33)
Current smoker	

	n (%) ^a
No	318 (93)
Yes	23 (7)
	Median (IQR)
Cycle day of positive pregnancy test	29 (27, 32)

^aMay not add to total due to missing data

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Table 2

Prevalence of Signs and Symptoms by Week Following Positive Pregnancy Test, Overall and by Pregnancy Loss Status Among Women in the LIFE Study, Michigan and Texas, USA, 2005–2009

	Number of ongoing pregnancies ^a	Overall (n=335) %	No Loss (n=245) %	Loss (n=90) %
No symptoms				
Week 1	335	13	13	12
Week 2	300	18	15	27
Week 3	288	14	13	20
Week 4	283	11	8	24
Week 5	271	13	12	25
Any bleeding				
Week 1	335	20	13	39
Week 2	300	16	14	24
Week 3	288	18	17	24
Week 4	283	19	18	29
Week 5	271	22	22	25
Light/moderate/heavy bleeding				
Week 1	335	13	7	29
Week 2	300	10	8	18
Week 3	288	8	8	11
Week 4	283	11	10	15
Week 5	271	10	10	9
Moderate/heavy bleeding				
Week 1	335	10	6	23
Week 2	300	7	5	17
Week 3	288	4	4	5
Week 4	283	6	7	6
Week 5	271	1	0	3
Any nausea and/or vomiting				
Week 1	335	75	72	81
Week 2	300	64	66	55
Week 3	288	78	81	62
Week 4	283	81	86	54
Week 5	271	81	83	58
Any vomiting				
Week 1	335	19	17	24
Week 2	300	14	14	18
Week 3	288	19	21	9
Week 4	283	22	25	6
Week 5	271	32	34	17
Nausea only ^a				
Week 1	335	56	55	57

	Number of ongoing pregnancies ^a	Overall (n=335) %	No Loss (n=245) %	Loss (n=90) %
Week 2	300	50	53	37
Week 3	288	59	61	53
Week 4	283	59	61	48
Week 5	271	49	50	41
Any cramping				
Week 1	335	72	69	77
Week 2	300	56	57	52
Week 3	288	48	51	29
Week 4	283	50	52	40
Week 5	271	53	56	33

^aNumber of ongoing pregnancies represents the denominator for each week

^bNausea, but not vomiting, during the week

Table 3

Cumulative Probability of Pregnancy Loss and Hazard Ratios by Occurrence of Signs and Symptoms Each Week Following Positive Pregnancy Test Among Women in the LIFE Study, Michigan and Texas, USA, 2005–2009

	Probability of loss (95% confidence interval)		Hazard Ratio (95% confidence interval)
	Presence of symptom	Absence of symptom	Presence vs. absence of symptom
Any bleeding			
Week 1	0.6 (0.5, 0.8)	0.2 (0.2, 0.3)	6.2 (3.8, 10.2)
Week 2	0.3 (0.2, 0.5)	0.2 (0.1, 0.2)	2.3 (1.2, 4.3)
Week 3	0.2 (0.1, 0.3)	0.1 (0.1, 0.2)	1.5 (0.8, 2.8)
Week 4	0.2 (0.1, 0.3)	0.1 (0.1, 0.2)	1.6 (0.9, 2.8)
Week 5	0.1 (0.0, 0.2)	0.1 (0.1, 0.2)	0.8 (0.4, 1.7)
Light/moderate/heavy bleeding			
Week 1	0.8 (0.6, 1.0)	0.2 (0.2, 0.3)	8.7 (4.7, 16.0)
Week 2	0.4 (0.2, 0.6)	0.2 (0.1, 0.2)	3.0 (1.4, 6.4)
Week 3	0.2 (0.0, 0.4)	0.2 (0.1, 0.2)	1.4 (0.5, 3.8)
Week 4	0.2 (0.1, 0.4)	0.1 (0.1, 0.2)	1.4 (0.6, 3.2)
Week 5	0.1 (0.0, 0.2)	0.1 (0.1, 0.2)	0.6 (0.2, 2.2)
Moderate/heavy bleeding			
Week 1	0.8 (0.6, 1.0)	0.2 (0.2, 0.3)	8.3 (4.2, 16.4)
Week 2	0.6 (0.3, 0.9)	0.2 (0.1, 0.2)	4.7 (2.0, 10.7)
Week 3	0.2 (0.0, 0.5)	0.2 (0.1, 0.2)	1.4 (0.3, 6.5)
Week 4	0.1 (0.0, 0.3)	0.1 (0.1, 0.2)	0.9 (0.2, 3.2)
Week 5	0.4 (0.0, 0.7)	0.1 (0.1, 0.2)	2.8 (0.7, 11.4)
Any nausea and/or vomiting			
Week 1	0.3 (0.2, 0.4)	0.2 (0.1, 0.3)	1.3 (0.9, 2.0)
Week 2	0.2 (0.1, 0.2)	0.2 (0.2, 0.3)	0.6 (0.4, 1.0)
Week 3	0.1 (0.1, 0.2)	0.3 (0.2, 0.4)	0.5 (0.3, 0.7)
Week 4	0.1 (0.1, 0.1)	0.3 (0.2, 0.5)	0.4 (0.2, 0.6)
Week 5	0.1 (0.1, 0.1)	0.2 (0.1, 0.4)	0.3 (0.2, 0.5)
Any vomiting			
Week 1	0.4 (0.2, 0.6)	0.2 (0.1, 0.3)	1.7 (0.8, 3.6)
Week 2	0.3 (0.1, 0.4)	0.2 (0.2, 0.3)	1.0 (0.5, 2.2)
Week 3	0.1 (0.0, 0.2)	0.3 (0.2, 0.4)	0.3 (0.1, 0.8)
Week 4	0.0 (0.0, 0.1)	0.3 (0.2, 0.5)	0.1 (0.0, 10.8)
Week 5	0.1 (0.0, 0.1)	0.2 (0.1, 0.4)	0.2 (0.1, 0.7)
Any nausea^a			
Week 1	0.3 (0.2, 0.4)	0.2 (0.1, 0.3)	1.2 (0.8, 1.9)
Week 2	0.1 (0.1, 0.2)	0.2 (0.2, 0.3)	0.5 (0.3, 0.9)
Week 3	0.1 (0.1, 0.2)	0.3 (0.2, 0.4)	0.5 (0.3, 0.8)
Week 4	0.1 (0.1, 0.2)	0.3 (0.2, 0.5)	0.4 (0.3, 0.7)
Week 5	0.1 (0.0, 0.2)	0.2 (0.1, 0.4)	0.4 (0.2, 0.7)

	Probability of loss (95% confidence interval)		Hazard Ratio (95% confidence interval)
	Presence of symptom	Absence of symptom	Presence vs. absence of symptom
Any cramping			
Week 1	0.3 (0.2, 0.4)	0.2 (0.1, 0.3)	1.8 (1.2, 2.7)
Week 2	0.2 (0.1, 0.2)	0.2 (0.1, 0.3)	0.9 (0.6, 1.5)
Week 3	0.1 (0.1, 0.1)	0.2 (0.1, 0.3)	0.5 (0.3, 0.9)
Week 4	0.1 (0.1, 0.2)	0.2 (0.1, 0.2)	0.6 (0.3, 1.0)
Week 5	0.1 (0.0, 0.1)	0.2 (0.1, 0.2)	0.4 (0.2, 0.7)

^a Nausea, but not vomiting, during the week

Table 4

Cumulative Probability of Pregnancy Loss and Hazard Ratios by Occurrence of Combinations of Signs and Symptoms Each Week Following Positive Pregnancy Test Among Women in the LIFE Study, Michigan and Texas, USA, 2005–2009

		Hazard Ratio (95% confidence interval)	
	Probability of loss (95% confidence interval)	Reference includes women with no symptoms or with spotting only	Reference includes women with no symptoms
No symptoms ^a			
Week 1	0.2 (0.1, 0.4)	1.0 (Reference)	1.0 (Reference)
Week 2	0.3 (0.2, 0.4)	1.0 (Reference)	1.0 (Reference)
Week 3	0.2 (0.1, 0.3)	1.0 (Reference)	1.0 (Reference)
Week 4	0.3 (0.2, 0.5)	1.0 (Reference)	1.0 (Reference)
Week 5	0.2 (0.1, 0.3)	1.0 (Reference)	1.0 (Reference)
Cramping only			
Week 1	0.2 (0.0, 0.3)	0.5 (0.1, 2.0)	0.5 (0.1, 2.2)
Week 2	0.2 (0.1, 0.3)	0.6 (0.2, 1.3)	0.6 (0.3, 1.4)
Week 3	0.2 (0.0, 0.3)	0.4 (0.1, 1.7)	0.6 (0.2, 2.2)
Week 4	0.2 (0.0, 0.4)	1.0 (0.4, 2.7)	0.6 (0.1, 2.8)
Week 5	0.3 (0.0, 0.5)	0.9 (0.2, 3.5)	1.0 (0.2, 4.0)
Nausea/vomiting only			
Week 1	0.2 (0.0, 0.3)	0.6 (0.2, 1.7)	0.7 (0.2, 1.9)
Week 2	0.1 (0.1, 0.2)	0.4 (0.2, 0.9)	0.5 (0.2, 1.1)
Week 3	0.2 (0.1, 0.2)	0.6 (0.4, 1.0)	0.7 (0.4, 1.1)
Week 4	0.1 (0.0, 0.2)	0.4 (0.2, 0.7)	0.4 (0.2, 0.8)
Week 5	0.1 (0.0, 0.2)	0.4 (0.2, 0.9)	0.4 (0.2, 0.9)
Nausea/vomiting + cramping			
Week 1	0.2 (0.1, 0.3)	0.9 (0.6, 1.6)	0.9 (0.5, 1.5)
Week 2	0.1 (0.1, 0.2)	0.5 (0.2, 0.9)	0.5 (0.3, 1.0)
Week 3	0.1 (0.0, 0.1)	0.2 (0.1, 0.6)	0.3 (0.1, 0.7)
Week 4	0.1 (0.0, 0.1)	0.3 (0.1, 0.6)	0.3 (0.1, 0.7)
Week 5	0.1 (0.0, 0.1)	0.2 (0.1, 0.5)	0.2 (0.1, 0.6)
Nausea/vomiting + cramping + bleeding			
Week 1	0.7 (0.5, 0.9)	5.2 (2.6, 10.5)	4.5 (2.4, 8.5)
Week 2	0.3 (0.1, 0.5)	1.6 (0.7, 3.8)	1.4 (0.6, 3.1)
Week 3	0.1 (0.0, 0.2)	0.5 (0.1, 2.2)	0.4 (0.1, 1.4)
Week 4	0.1 (0.0, 0.3)	0.5 (0.2, 1.8)	0.5 (0.2, 1.5)
Week 5	0.1 (0.0, 0.1)	0.0 (0.0, 229)	0.2 (0.1, 1.0)

^aNo symptoms includes women without any cramping, bleeding, nausea and/or vomiting