A prospective study of the onset of symptoms of pregnancy

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Abstract

The objective of this study was to provide prospectively collected data on the onset of pregnancy symptoms. Two hundred twenty-one women attempting pregnancy kept daily records of the occurrence of symptoms of pregnancy. Among 136 women delivering live infants, half began experiencing symptoms by day 36 after their last menstrual period (LMP), and 89% by the end of the eighth week. Onset of symptoms occurred later in pregnancies that went on to miscarry. Among 48 women with biochemically detected pregnancy loss before 6 weeks LMP, symptoms were substantially reduced but not entirely absent. Women who smoked tobacco or marijuana tended to have delayed onset of symptoms. Nearly 90% of women with successful pregnancies experience symptoms within 8 weeks LMP. Even pregnancies lost very early (before 6 weeks) are sometimes symptomatic. The earliest symptoms do not begin until after key stages of embryogenesis, reinforcing the need for women to initiate sound health behaviors before pregnancy is apparent. Published by Elsevier Science Inc.

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1. Introduction

The first indication of pregnancy is typically the absence of menses, usually followed by symptoms that include nausea, vomiting, fatigue, frequent urination, and breast tenderness and swelling [1]. These symptoms can be so severe as to be debilitating [2,3]. Although unpleasant, symptoms may protect women from ingesting substances that could damage the embryo during the crucial early stages of development [4,5]. Furthermore, by alerting women to the fact of pregnancy, symptoms may prompt women to change their behaviors to protect their fetus, and to seek prenatal care.

Because little is known about the natural history of early pregnancy, pregnant women and their physicians do not always know what to expect with regard to symptoms. Data on symptoms in early pregnancy help provide norms for a health event that affects about 6 million women each year in the United States. Knowledge about the timing of onset of symptoms may also be useful to researchers in the design of clinical trials for drugs to treat the nausea and vomiting of early pregnancy.

The emergence of symptoms early in pregnancy has not previously been well described. Studies have typically enrolled women after clinical confirmation of pregnancy, sometimes late into the first trimester [3,6–9], with informa-tion about the onset of symptoms based on women's recall. We provide detailed data on the emergence of pregnancy symptoms, as recorded prospectively by women who began collecting daily information before they became pregnant.

2. Methods

The North Carolina Early Pregnancy Study was a prospective cohort study of 221 women, conducted from 1982 to 1985. Women were required to be planning a pregnancy and to have no history of fertility problems. Ninety-six percent were White, median age was 29 years (range 21–42), 71% were college educated, and 35% had never been pregnant. The study was approved by the institutional review board of the National Institute of Environmental Health Sciences, and all women provided informed consent. Details of the data collection and laboratory methods have been described previously [10,11].

Women participated from the time they stopped using any method of birth control until 8 weeks past their last menstrual period (LMP) if they became clinically pregnant, or for up to 6 months if they did not. Each woman collected daily first morning urine specimens, which were transferred into permanent storage at −20°C. Urine specimens were collected for 98% of the study days.

Ovulation was identified using measurements of estrogen and progesterone metabolites in urine [12]. Pregnancy was identified using a highly sensitive and specific immunoradiometric assay to detect an increase in urinary human

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chorionic gonadotropin (hCG) [13]. We considered a pregnancy to have occurred if urinary hCG exceeded 0.025 ng/mL for at least 3 consecutive days. Pregnancies that ended in loss 6 weeks or more after the last menstrual period were considered clinical miscarriages; those ending earlier were considered early (subclinical) losses. The day of the loss was defined as the first day of vaginal bleeding associated with the fall of hCG. We defined "early" loss by the time between LMP and onset of bleeding, so that the definition could be easily replicated in other studies. Most pregnancies ending in early loss were unrecognized by the women or their physician, but not all. All hormone assays were performed after completion of the field study.

At the time of daily urine collection, each woman recorded whether or not she had had symptoms of pregnancy in the previous 24 hr, noting "Y" (yes) or "0" (no) on the diary record card. This provided data on the presence or absence of symptoms that the women thought might be due to pregnancy, without specifying the type of symptoms. Symptoms occurring "in the previous 24 hours" were assigned to the day on which information was recorded. The presence (or absence) of symptoms of pregnancy was recorded for 98% of days. Ninety-nine percent of women with clinical pregnancies provided data for at least 7 weeks after LMP, and 96% collected data for 8 weeks.

At the time of enrollment into the study, women were interviewed about their reproductive history, use of alcohol, tobacco, and marijuana, and other exposures. This information was updated after 3 months for women who had not become clinically pregnant.

At study completion women were asked to report the date of any positive pregnancy test. Because this question was added to a later version of the interview, this information is available for only two-thirds of the women. All women who became clinically pregnant were contacted later to determine the outcome of the pregnancy.

Data were collected on 723 menstrual cycles, including 524 nonconception cycles, 136 cycles ending in live births, 15 clinical miscarriages, and 48 early losses. A date of ovulation was identified for the conception cycle of 129 of the 136 live births, and for all clinical miscarriages and early losses.

Although "symptoms" were noted sporadically in nonconception cycles, the typical onset of symptoms was abrupt and sustained. Therefore, we required 3 consecutive days of symptoms to qualify as "symptoms of pregnancy," with the first of those days being the day of onset of symptoms. Because of missing data, an exact date of symptom onset was uncertain for three women with clinical pregnancies. For these women the onset date was assigned as the earliest *recorded* 3-day sequence of symptoms.

Because our sample included pregnancy losses and nonconception cycles (which have fewer possible days for symptoms to occur before another menses), we used life-table methods to estimate the cumulative probability of symptom onset. This was done separately for pregnancies ending in live birth, clinical loss, early loss, and for cycles with no detected conception. Symptom onset times were treated as censored at the time of onset of bleeding (due either to the return of menses if there was no conception, or to pregnancy loss).

We also looked at factors that might accelerate or delay onset of symptoms. Information on alcohol, tobacco, and marijuana use was taken from the 3-month interview if available; otherwise, information was taken from the enrollment interview. A simple analysis of factors affecting the presence or absence of symptoms could give biased results because longer menstrual cycles would offer more opportunity for symptoms to be reported. We accounted for differential follow-up using Cox regression models to model time to onset of symptoms. The relative risk provides an estimate of the relative hazard of the onset of symptoms of pregnancy on a particular cycle day, comparing women with and without the factor under consideration. (Relative risks less than 1.0 indicate a later onset of symptoms).

3. Results

The 3-day criterion for onset of symptoms identified a time of abrupt increase in symptoms for clinical pregnancies. Among women with clinical pregnancies, symptoms were reported on only 3% of days in the week preceding onset but on 94% of days in the week following.

Figure 1 shows the time of onset of symptoms for various categories of pregnancy and for nonconception cycles. Women reported 3 or more consecutive days of symptoms in 9% of nonpregnant cycles. This provides a "background" level of false-positive symptoms against which the true positives must be measured. By cycle day 27, women with successful pregnancies started reporting symptoms above this background level. Most women reported onset of symptoms in their fifth or sixth weeks (59% on days 29–42), with a total of 71% reporting symptoms by the end of 6 weeks (day 42),
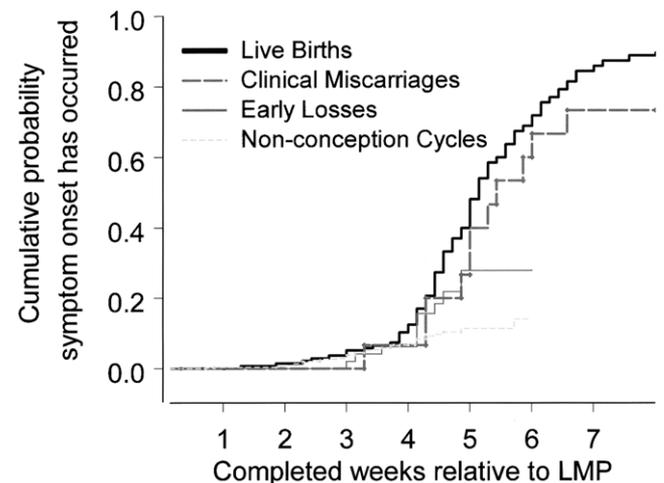
Fig. 1. Timing of onset of symptoms of pregnancy for women with live births, clinical miscarriages, early losses, and nonconception cycles.

and 89% by 8 weeks (day 56). Half of women with successful pregnancies reported symptoms by day 36.

We also looked at the onset of symptoms of pregnancy in relation to the time of ovulation, which is less variably distant from the time of implantation than is LMP. Half of the women with successful pregnancies reported symptoms within 20 days after ovulation, with an interquartile range of 11 days. This is less than the interquartile range with LMP (13 days), presumably reflecting the fact that some of the variation in timing of symptom onset in relation to LMP reflects the varying lengths of women's follicular phases.

Of the 15 women whose pregnancies ended in clinical miscarriage, 10 (67%) reported an onset of symptoms by 6 weeks (day 42) after LMP (Fig. 1). At any given time relative to LMP, proportionately fewer women with pregnancies ending in clinical loss reported symptoms compared with women with successful pregnancies (RR = 0.7, 95% CI = 0.4–1.2).

Symptoms of pregnancy were reported in only 21% of pregnancies that ended in early loss. Among early losses that ended within 4 or 5 weeks after LMP, 14% had a symptom onset, while among those ending during the sixth week, 45% had a symptom onset. The day-specific likelihood of symptom onset was lower among early losses than among successful pregnancies (RR = 0.5, 95% CI = 0.3–1.0), but higher among early losses than among the nonconception cycles (RR = 2.0, 95% CI = 1.0–4.0).

Many women began to report the presence of symptoms around the time they were expecting their period. This raises the possibility that nonspecific symptoms may be interpreted as "symptoms of pregnancy" if they occur in combination with delayed menses. We therefore conducted a more detailed analysis of false-positive symptoms among nonconception cycles. At enrollment, women had reported whether their menstrual cycles were generally regular or irregular. Women also provided their usual cycle length (defined as the number of days from the first day of one menstrual period to the first day of the next). We stratified symptom onset in nonconception cycles according to whether the next menses was 1 or more days earlier than expected, 1 to 6 days later than expected, or 7 or more days later than expected. Among women with generally regular menstrual cycles, false-positive onset of symptoms was reported in 6, 8, and 22% of cycles where the next menses was early, slightly late, or very late. In comparison, among early loss cycles, symptom onset was reported in 17, 17, and 45% of cycles where the loss was early, slightly late, or very late relative to the expected date of menses. Thus, delayed menses presumably contributed somewhat but not entirely to the report of earliest symptoms among women who were pregnant.

Some nonpregnant women may have misinterpreted premenstrual symptoms as symptoms of pregnancy. To examine this possibility, we looked at the presence of symptoms in nonconception cycles just prior to the actual onset of menses. We excluded cycles that were longer than the woman's usual cycle length, so that any increase in symptom reporting just before menses could not be due to mistaking delayed menses for pregnancy. Symptoms were reported on 6% of woman days in the week prior to menses, compared with 2% of woman days in the second week prior to menses and fewer than 1% of woman days in the third week prior to menses. Thus, premenstrual symptoms may account for some false-positive symptoms of pregnancy that would not be expected to occur in pregnant women.

Because these women were attempting to become pregnant, many had pregnancy tests relatively early. It is possible that a positive pregnancy test would make women more likely to report the presence of symptoms of pregnancy. To examine this, we looked at symptoms in relation to the date of the positive pregnancy test. Among women with symptoms, 79% had their onset of symptoms before their pregnancy test. This suggests that symptoms led to the pregnancy test, rather than vice versa.

We looked at factors that might affect the onset of symptoms, including whether the woman had previously been pregnant or given birth; use of tobacco, marijuana, or alcohol; the woman's age, body mass index, and employment status; and sex of the infant (Table 1). This analysis was confined to women whose current pregnancy ended with live birth. Women who had had a previous pregnancy of any kind reported slightly earlier onset of symptoms. This association was not present when we compared women with and without a previous live birth.

Table 1
Association of factors with timing of onset of symptoms of pregnancy in relation to LMP, among women with live births (each entered separately in the model)

Variable	n	RR	95% CI	P-value
Parity				
Previous live birth	68	1.01	(0.71–1.44)	0.96
No previous live birth	68			
Gravidity				
Previous pregnancy	88	1.28	(0.88–1.87)	0.20
No previous pregnancy	48			
Age				
32–42 years	30	1.13	(0.74–1.74)	0.57
21–31 years	106			
Smoker				
Yes	7	0.53	(0.21–1.29)	0.16
No	129			
Recent marijuana use				
Yes	15	0.68	(0.38–1.21)	0.19
No	121			
Top 20% of body mass index				
Yes	25	1.14	(0.73–1.80)	0.57
No	111			
Employed				
Yes	90	0.85	(0.59–1.24)	0.41
No	46			
Alcohol				
8+ drinks/month	61	0.98	(0.68–1.40)	0.89
7 or fewer	75			
Infant sex				
Girl	64	0.87	(0.61–1.25)	0.46
Boy	72			

There was a tendency for women who smoked tobacco or marijuana at the time of enrollment to have a delayed onset of symptoms of pregnancy. Median time of onset of symptoms among marijuana smokers was day 42, compared with day 35 for other women. This delay in symptoms could be a reflection of later ovulation caused by marijuana or tobacco smoking. We addressed this by reanalyzing onset of symptoms in relation to time of ovulation, and the delay in symptoms with tobacco or marijuana use persisted. When the association between tobacco and symptom onset was controlled for marijuana use, and vice versa, results were unchanged.

Prior studies suggested an association of more severe symptoms with female babies [14,15]. There was no association in our data between infant sex and the onset of symptoms. We previously observed that cycles leading to female births had longer follicular phases [16]. To remove the influence of follicular phase length, we recalculated symptom onset for female vs. male fetuses in relation to ovulation. Results were unchanged (RR = 1.0, 95% CI = 0.7–1.5).

4. Discussion

Eighty-nine percent of women with live births experienced the onset of symptoms of pregnancy within the first 8 weeks after LMP. This is roughly consistent with other studies that collected prospective information on nausea, a common symptom of pregnancy [3,7,9]. However, because previous studies did not begin collecting data until after pregnancy had been diagnosed, any information on the timing of the onset of symptoms has necessarily been based on recall. In our study, half of women with successful pregnancies had symptoms by cycle day 36, which is earlier than reported for the onset of nausea by Gadsby et al. [3] (approximately day 43), Tierson et al. [7] (approximately week 6, days 36–42), and Lacroix et al. [9] (approximately week 7, days 43–49). The earlier onset found in our study could also be due to symptoms other than nausea, if such symptoms occur earlier in pregnancy.

Mild and moderate nausea and vomiting during pregnancy has been associated with a lower risk of miscarriage [6,17–19]. This was supported by our data; day-specific onset of symptoms tended to be less likely for pregnancies ending in clinical miscarriages compared with live births (RR = 0.7, 95% CI = 0.4–1.2).

In this study, there were 48 biochemically diagnosed very early losses, which are sometimes referred to as "subclinical pregnancies" [20]. Women reported the presence of symptoms of pregnancy in one out of five of these pregnancies. In part, the low rate of symptoms is due to the brief duration of these pregnancies, which provided a reduced opportunity for symptoms to occur. However, the difference was confirmed with life table analysis that adjusts for this difference. Also, symptoms were reported more often for early loss cycles than for nonconception cycles, suggesting

that at least a few of these "subclinical" pregnancies could be at least transiently recognized by the women themselves.

Nonsmokers appeared to be more likely than smokers to report symptoms of pregnancy, a finding consistent with previous studies of nausea and vomiting during pregnancy [6,15,21,22]. In contrast with some previous studies, we did not find symptoms to be associated with nulliparity, younger age, or higher body mass index [6,15,18,21], although we cannot exclude the possibility of modest associations.

A recent study of Swedish births reported that hospital admission in the first trimester for hyperemesis gravidarum was associated with delivery of a female infant [14]. We did not find any association between sex of the baby and the timing of symptom onset.

Marijuana use appeared to be associated with a delay of onset of symptoms of pregnancy. Later recognition of pregnancy among marijuana users has been reported at least once before [23]. This result is not implausible. Marijuana is known to decrease nausea resulting from chemotherapy treatment for cancer [24,25], and it may have similar effects on nausea from other causes. However, women should not be advised to use marijuana for this purpose. The effects of marijuana on the developing fetus are not well studied, but there is some evidence for adverse effects on the developing nervous system [26]. There are other, presumably safer strategies to manage nausea and vomiting during pregnancy, including antiemetic medications and dietary and lifestyle changes [27].

Half of all women with successful pregnancies had not begun to have symptoms by the 20th day of embryonic life (that is, 20 days after ovulation). By the 20th day, the central nervous system and heart have begun to develop, and are susceptible to teratogens [28]. Given that a substantial number of pregnancies in the United States are unplanned [29] and the natural variability of the menstrual cycle [30], the onset of symptoms may be the first time a women recognizes that she is pregnant. Any postponement in onset of the symptoms may delay actions that a woman might make for the protection of her embryo, such as a change of occupational duties to reduce exposure to possible hazards, or the cessation of smoking or alcohol consumption. It is ironic that tobacco consumption itself may act to delay women's perception of pregnancy.

We estimate that 89% of women who go on to deliver live infants develop sustained symptoms of pregnancy in the first 8 weeks following the first day of the LMP. This relatively high frequency may reflect the fact that women in our study recorded the presence of any symptoms of pregnancy, which would include symptoms other than nausea or vomiting. Additionally, women who are attempting pregnancy may be more likely to report symptoms earlier in pregnancy (or even when not pregnant). However, the incidence of symptoms in nonconception cycles was relatively uncommon.

In conclusion, this prospective study showed that most pregnant women reported symptoms by the end of the sixth week after LMP; symptoms started abruptly and continued daily. Although women with very early pregnancy losses were

less likely to report symptoms than women with continuing pregnancies, they, nonetheless, had more symptoms than women who were not pregnant at all. Thus, "subclinical" pregnancies were not entirely unrecognized by the women themselves.

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