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Is opioid use safe in women trying to conceive?

Kerry S. Flannagan[1], **Sunni L. Mumford**[1], **Lindsey A. Sjaarda**[1], **Jeannie G. Radoc**[1], **Neil J. Perkins**[1], **Victoria C. Andriessen**[1], **Jessica R. Zolton**[1,2], **Robert M. Silver**[3], **Enrique F. Schisterman**[1]

[1]Epidemiology Branch, Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA

[2]Program in Reproductive Endocrinology and Gynecology, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA

[3]Obstetrics and Gynecology, School of Medicine, University of Utah, Salt Lake City, UT, USA

Abstract

Background: Opioids are commonly prescribed to women of reproductive age, including after delivery and miscarriage. However, to our knowledge, opioid use has not been frequently studied in relation to the common reproductive complications of impaired fecundability and pregnancy. We examined the association of opioid use during the critical window of pregnancy establishment with fecundability and pregnancy loss.

Methods: We measured opioid use by urine screening and self-report at multiple time points during preconception and early pregnancy in a prospective cohort of women attempting conception (n=1228). The main outcomes included time to hCG-detected pregnancy and incidence of live birth and pregnancy loss. We estimated fecundability odds ratios (FOR) and risk ratios (RR) with 95% confidence intervals (CI) adjusting for sociodemographic characteristics, reproductive characteristics, and use of antidepressants, tobacco, alcohol, and marijuana.

Results: Prevalence of preconception opioid use was 18% (n=226 of 1228), and in early pregnancy was 5% (n=33 of 685). Opioid use while attempting pregnancy was associated with reduced fecundability (FOR: 0.71; 95% CI: 0.50, 1.0). Risk of pregnancy loss increased as opioid exposure was detected later in gestation, from the beginning of the cycle of conception (RR: 1.5; 95% CI 0.85, 2.6), to week 4 of pregnancy (RR: 2.1; 95% CI: 1.1, 4.1), and to week 4 and 8 of pregnancy (RR: 2.5; 95% CI: 1.3, 5.0).

Conclusions: Our results are consistent with the hypothesis that opioid exposure while trying to conceive may be harmful, even among healthy, non-opioid-dependent women. Possible risks to

Correspondence: Enrique F. Schisterman, Ph.D., Epidemiology Branch, Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, 6710B Rockledge Drive, MSC7004, Bethesda, MD 20894 (schistee@mail.nih.gov; tel 301-435-6893) .

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fecundability and pregnancy viability are relevant to patients and providers when evaluating pain management approaches.

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Keywords

opioids; fertility; fecundability; pregnancy loss; live birth

INTRODUCTION

In the US, one in five women of reproductive age are exposed to prescription opioids.[1] In 2017, use among these women was higher than in the general US population.[1] As prescription opioid use has become widespread,[2] an explosion of research related to opioids in the past decade has focused on dependency and its effects, while opioid research in the field of reproduction has mainly focused on fetal harms among opioid-dependent women.[3,4]

Meanwhile, opioids are frequently prescribed to women after common obstetric procedures, such as to new mothers after cesarean or vaginal delivery,[5,6] or to women undergoing dilation and curettage following a miscarriage.[7] However, despite the likelihood of exposure among women of reproductive age and especially those who have previously been pregnant and may wish to become pregnant again, there is almost no data on the reproductive effects of opioid use. Only one study has examined the association between self-reported opioid use and fertility, reporting lower fecundability among opioid users.[8] It remains unclear whether opioid use around the time of conception could affect risk of pregnancy loss, the most common complication of pregnancy which affects 20%−30% of conceptions and has few known causes. Furthermore, previous studies have not assessed episodic, non-chronic opioid use, which is more common than chronic or dependent use[9] and likely especially common in generally healthy populations. Given the potential for harm, and that maternal exposures during the vulnerable periconception period can affect both maternal and fetal health, it is important for women and their healthcare providers to understand potential reproductive risks when determining whether prescription opioids are appropriate for pain management.

Our objective was to evaluate the association of opioid use at multiple critical points surrounding the establishment of pregnancy with reproductive outcomes. Specifically, we assessed opioid use while trying to conceive in relation to fecundability and live birth, and opioid use shortly before conception and during early pregnancy in relation to pregnancy loss. We conducted this investigation in a longitudinal study of women attempting pregnancy who were healthy, without infertility, and generally free of indications for chronic opioid use.

METHODS

Study population

This was a secondary analysis of the EAGeR trial, a randomized, blinded, placebo-controlled trial of low-dose aspirin to improve live birth rates. The original study was conducted in a cohort of 1228 women who were recruited from four clinical sites in the US

between 2007 and 2011 while attempting natural conception. Details of the study have been described.[10,11] Participants were 18–40 years old, had one to two previous pregnancy losses, were healthy without major medical disorders, and had no history of treatment for infertility or infertility-related conditions including endometriosis and polycystic ovary syndrome. Women were followed for up to six menstrual cycles or throughout pregnancy if they conceived. The original trial was registered with ClinicalTrials.gov (#NCT00467363). Procedures were approved by institutional review boards at each study site and the data coordinating center. Participants provided written informed consent prior to participation.

Data collection

Women completed study clinic visits at baseline and the end of each menstrual cycle with questionnaire and biospecimen collection. At baseline, participants completed questionnaires on demographics, socioeconomic and lifestyle characteristics, and health and reproductive history. Study staff measured height and weight using standardized protocols and body mass index (BMI) was calculated as kg/m^2. Women who became pregnant recorded the severity of any abdominal pain and cramping in daily diaries during early pregnancy. Severity was recorded on a scale of 0 to 3, with 0 representing no pain or cramping and 3 representing most severe pain and cramping.

Definition of exposures

We assessed opioid use by urine measurement via chemiluminescent immunoassays (Drugs of Abuse Ultra and Drugs of Abuse IV, Randox Toxicology, County Antrim, UK) for the following opioids and their metabolites: oxycodone, hydrocodone, noroxycodone, oxymorphone, codeine, dihydrocodeine, hydromorphone, morphine, desomorphine, heroin, levorphanol, thebaine, tramadol, fentanyl, methadone, and buprenorphine. Samples were considered positive for each analyte if concentrations were above manufacturer-recommended cutoffs. We defined a positive opioid measurement as being positive for any tested opioids. These biochip assays contain eight individual tests that detect different opioids, and all tests were performed on each urine sample. Some tests measure multiple opioids without distinguishing between them, and these groups are listed in eFigure 1.

We obtained self-reported opioid use from questionnaires. At baseline, women were asked to report any medications used prior to or during their last pregnancy before study enrollment, and the indication for use. The median (25^{th} percentile, 75^{th} percentile) time between the last pregnancy and study baseline was 15.7 (8.0, 37.1) weeks. We defined self-reported opioid use as use of any medication containing an opioid other than dextromethorphan.

In the analyses, we assessed opioid exposure at multiple times throughout preconception and early pregnancy. We considered urine opioid measurement at baseline, the beginning of the cycle resulting in conception, any time before conception (including baseline and the beginning of the conception cycle), week 4 of pregnancy, and any time during early pregnancy (including weeks 4 and 8 of pregnancy). When more than one measurement contributed to a specific exposure, women were considered exposed if at least one measurement was positive. We also used combined exposures in which women were

considered exposed if they had either urine-measured or self-reported use at any time before conception.

Definition of outcomes

The primary outcomes were time to human chorionic gonadotropin (hCG)-detected pregnancy, and incidence of live birth and pregnancy loss. As previously described,[10,12] pregnancies were identified by 1) a positive urine pregnancy test (Quidel Corporation, San Diego, CA) sensitive to 25 mIU/mL hCG, which was conducted on spot urine samples at end-of-cycle clinic visits when a participant reported missing menses, or by 2) free beta-hCG testing performed on daily first-morning urine samples from the last 10 days of the first two study cycles and on spot urine samples from all end-of-cycle visits (Diagnostic Automation, Inc., Calabasas, CA; BioVendor, Asheville, NC). This testing allows for more sensitive detection of very early pregnancies compared to conventional pregnancy tests.[10] Live birth was ascertained through medical records. Pregnancy loss included hCG-detected losses and clinically recognized losses. HCG-detected losses were defined in two ways: a positive hCG pregnancy test at home or the clinic followed by a lack of clinical signs of pregnancy at the study ultrasound, or a positive free beta-hCG test followed by a lack of positive pregnancy test at home or the clinic.[10] Clinically recognized losses were all losses detected after ultrasound confirmation of pregnancy, including pre-embryonic, embryonic, ectopic, and fetal losses, and stillbirths.

Statistical analysis

The analytic sample for analyses of fecundability included all 1228 women enrolled in the EAGeR cohort. While 10 of these women did not have available biospecimens for opioid measurement, in all regression models we used multiple imputation with fully conditional specification to account for missing exposure and covariate data; thus women were included in analyses even if they had missing data on urine opioid measurement. For live birth, 1088 women who completed follow-up were included (N=1081 with urine opioid measurement) and for analyses of pregnancy loss we included 785 women who had complete follow-up and became pregnant (N=778 with urine opioid measurement). The flow of participants is described in eFigure 1. We estimated percentages and means (±standard deviation [SD]) of sociodemographic characteristics among women with and without preconception opioid exposure.

To assess time to pregnancy, we estimated fecundability odds ratios (FOR) and 95% confidence intervals (CI) comparing opioid users vs. non-users with discrete time Cox proportional hazard models. An FOR <1 indicates decreased fecundability or a longer time to pregnancy. These models account for right censoring among women who did not complete follow-up left truncation or immortal time bias as a result of women entering the study after different lengths of time spent trying to conceive. In our primary analysis, we considered opioid use by urine measurement at baseline. In additional analyses we also considered opioid use at any time before conception, in order to capture women who may have been using opioids but did not test positive at the baseline measurement, given the short half-life of these medications in urine.[13] In multivariable analysis we estimated FOR adjusted for age, race, BMI, education level, physical activity, smoking and alcohol use,

marijuana use and antidepressant use measured by self-report or urine immunoassay, number of prior pregnancy losses, the time since a woman's last pregnancy, whether a woman self-reported a gynecological indication for opioid use (cramps, ovarian cysts, or uterine fibroids), and the typical severity of abdominal cramping and back pain during menstrual periods over the past year. We also conducted supplemental analyses further adjusting for study treatment arm.

In analysis of live birth and pregnancy loss, we estimated risk ratios (RR) and 95% CI comparing opioid users vs. non-users with Poisson regression models. Multivariable models included the same covariates described above. In addition to the preconception opioid use measures, in models of pregnancy loss we also considered urine measurement at the beginning of the conception cycle, and urine measurement at week 4 and week 4 or 8 of pregnancy. Because opioid use may be associated with loss to follow-up, we used inverse probability of retention weights in all models to account for possible selection bias. We restricted models of pregnancy loss to women who became pregnant (or, for early pregnancy exposure, to women who had a pregnancy lasting at least 4 or 8 weeks) and used inverse probability of pregnancy weights to account for possible selection bias from these restrictions. Models of early pregnancy opioid use and pregnancy loss also accounted for preconception opioid use and for severity of abdominal pain and cramping in the two weeks preceding opioid measurement, as reported by women in daily diaries during early pregnancy.

In order to ensure that our analysis accounted for potential confounding, especially confounding by indication, we also conducted sensitivity analyses in which we adjusted for confounders using propensity score matching. We derived propensity scores from models of each opioid exposure with all confounders as predictors. We used 2:1 greedy matching without replacement and conducted analyses accounting for matching among participants included in the matched sets.

We conducted analyses using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Before conception, 110 women (9%) had positive urine measurement of opioids, 141 (12%) reported opioid use during or prior to their last pregnancy, and 226 (18%) had either urine-measured or self-reported use. Among 683 women who had pregnancies lasting at least 8 weeks, 33 (5%) had positive urine detection of opioids during early pregnancy. Of 250 women who tested positive in urine or self-reported at any time during follow-up, 84% did so once, 12% twice, and 4% three or four times. The most commonly reported opioids were hydrocodone and oxycodone (eFigure 2). The most common indications for self-reported past opioid use were pain after a past miscarriage (38% of all reports) and musculoskeletal pain (13%). Postpartum pain accounted for 4% of all reports. Women who tested positive for opioid use during pregnancy reported similar average severity of abdominal pain and cramping in the 2 weeks preceding pregnancy urine opioid measurement (median: 0.00; 25^{th}, 75^{th} percentile: 0.00, 0.50) as women who did not test positive for opioid use during pregnancy (median: 0.06; 25^{th}, 75^{th} percentile: 0.00, 0.44).

Sociodemographic correlates of opioid use

Compared to women without preconception opioid exposure, women with exposure were younger, less likely to have more than a high school education, more likely to have smoked in the past year, more likely to use antidepressants, more likely to have used opioids during or prior to their last pregnancy, had more severe pain during menstrual periods, were less likely to have had a live birth from their most recent pregnancy, and were more likely to withdraw from follow-up (Table 1). Treatment arm in the original study was not associated with overall preconception opioid use (49% assigned to low-dose aspirin among opioid-exposed women, 50% assigned to low-dose aspirin among the unexposed).

Fecundability

797 (65%) participants became pregnant during the six cycles of study follow-up. In our primary analysis, opioid use at baseline was associated with reduced fecundability (FOR: 0.71; 95% CI: 0.50, 1.0) (Table 2). Analysis of opioid use at any time during follow-up was also indicated similarly lower fecundability among opioid users (0.75; 95% CI: 0.55, 1.0). Further adjustment for treatment arm did not change the results (FOR, baseline opioid use: 0.72; 95% CI: 0.50, 1.0). Adjustment using propensity scores gave similar point estimates, although they were imprecise (eTable 1).

Live birth

There were 597 (55%) live births among all participants. Although point estimates suggested lower probability of live birth among opioid users, the estimates of association between live birth and opioid use at baseline were imprecise (RR: 0.87; 95% CI: 0.63, 1.2, Table 3). Results were similar when we considered opioid use at any time while attempting conception (RR: 0.85; 95% CI: 0.63, 1.2, Table 3). Adjustment for study treatment arm did not affect the results (RR, baseline opioid use: 0.87; 95% CI: 0.62, 1.2). Results using propensity score matching were similar to those from traditional regression (eTable 1).

Pregnancy loss

Among 785 pregnancies, 188 (24%) resulted in a loss. Opioid exposure at baseline was not associated with risk of loss (Table 4). However, risk of pregnancy loss increased as opioid exposure was detected later in gestation, ranging from the beginning of the cycle of conception (RR: 1.5; 95% CI 0.85, 2.6), to week 4 of pregnancy (RR: 2.1; 95% CI: 1.1, 4.1), and week 4 or 8 of pregnancy (RR: 2.5; 95% CI: 1.3, 5.0). Results from analyses using propensity score matching were similar although less precise (eTable 1).

DISCUSSION

In this preconception cohort study, our findings are consistent with the hypothesis that opioid exposure while trying to conceive may be harmful, even among healthy, non-opioid-dependent women. We found that opioid use while trying to conceive was associated with lower fecundability, and use in early pregnancy was associated with a more than twofold higher risk of pregnancy loss. Our novel longitudinal study addresses crucial gaps in the literature by including measures of opioid exposure assessed using urine measurement at critical periods throughout preconception and early pregnancy. Our results highlight the

public health relevance of opioid prescription among women of reproductive age. Indeed, women who are trying to conceive or might already be pregnant may incur important reproductive risks beyond more commonly considered outcomes such as opioid dependence or neonatal abstinence syndrome.

We found that opioid use while trying to conceive was associated with reduced fecundability. This is consistent with a previous large preconception study of North American women in which self-reported opioid use was associated with lower fecundability.[8] We were able to expand on this study by use of urine measurement of opioids during multiple critical windows for pregnancy establishment. Opioids may adversely affect endometrial receptivity to pregnancy[14] and exert harmful endocrine effects. Opioids act on the hypothalamic-pituitary-gonadal axis by centrally binding to μ-receptors in the hypothalamus, interrupting the pulsatile release of gonadotropin-releasing hormone directly[15,16] and indirectly through the increase of prolactin.[17] This causes disrupted production of luteinizing hormone and downstream effects on gonadal function and hormone synthesis, which could reduce fertility and libido.[18] Taken together, if shown to be causal, these findings suggest that for women who are attempting pregnancy, even short-term or episodic opioid use could adversely affect fecundability.

Importantly, the most novel finding of our study suggests the possibility of an increased risk of pregnancy loss as an unintended consequence of opioid use around the time of pregnancy establishment. Specifically, we observed increasingly higher risk of loss among opioid users as opioid exposure was detected later in gestation, ranging from 50% greater risk among users with opioid exposure at the beginning of the cycle of conception, to 110% at week 4 of pregnancy, and 150% at week 4 or 8 of pregnancy. In contrast, exposure at or prior to study enrolment was not associated with loss, implying that exposure specifically during the periconception window is an important risk factor for loss. While it is possible that women already undergoing a pregnancy loss might experience pain and be prescribed opioids as a result, this reverse causation is a less plausible explanation for our findings given that the association is already present with preconception use, and becomes steadily stronger throughout the prospectively monitored peri-conception period in a dose–response manner. Though exposure measured during the periconception time window has not been specifically explored previously, these findings are consistent with the positive association known between perinatal opioid dependency or poisoning and stillbirth risk.[19]

In this population, the majority of those who used opioids only did so once during the study, and none used methadone or buprenorphine, drugs typically employed in the treatment of opioid dependence. In addition, the prevalence of opioid use by any measure in this cohort was 18%, lower than the 27.7% annual prevalence of filled opioid prescriptions estimated among U.S. reproductive-age women during the same time period.[20] Taken together, this evidence suggests that opioid use in our study population is not representative of opioid dependency, and likely represents short term use of opioids for a variety of indications. Over one-third of the self-reported indications for past opioid use in this cohort were related to pain after miscarriage or delivery. Similarly, 19% of gynecologists in 2015–2016 reported prescribing opioids after dilation and curettage procedures,[7] and prescriptions are common after vaginal (29%)[21] and cesarean deliveries (85%).[5] Collectively, these data indicate that

questions about opioid prescribing practices are relevant to otherwise healthy women, especially those who may attempt pregnancy again soon, such as after pregnancy loss.

Our study presents novel and detailed data on preconception and early-pregnancy opioid use longitudinally in relation to reproductive outcomes. Importantly, our prospective assessment of outcomes, particularly pregnancy loss, enabled detection of early losses that are often not captured in studies that recruit women in early pregnancy. The use of urine measurement reduces the likelihood of exposure misclassification through underreporting of opioid use. Though urine measurement may miss some opioid use because of the short half-life of opioids in urine[13] and may misclassify some unexposed women as exposed due to false positives resulting from poppy seed ingestion or antibiotic use,[22] misclassification should be non-differential by outcome. Our study population was primarily white and of high socioeconomic status which may limit generalizability. However, we were able to adjust for multiple important confounders including use of antidepressants, tobacco, and marijuana. Though there is a potential concern of confounding by indication, we importantly adjusted for several factors related to gynecologic pain and fertility-related conditions, including menstrual pain, number of prior losses, as well as excluding women treated for endometriosis by design. Further, though pain, gynecologic or otherwise, could affect intercourse frequency and in turn fecundability, we observed no differences in reported intercourse frequency by opioid exposure status. Nevertheless, our findings may still be biased by confounding by indication or reverse causation. In particular, our finding of greater loss risk associated with opioid use during pregnancy could be influenced by women experiencing pain as part of an ongoing pregnancy loss and taking opioids to manage this pain. Our secondary analyses of fecundability and live birth in relation to opioid exposure at any time during follow-up may be subject to immortal time bias, since this exposure definition includes an assessment of opioid use that occurred while time to pregnancy was being accrued. Reassuringly, however, the point estimates obtained from these analyses were similar to the primary analyses in which exposure was measured only at baseline, which should not be subject to this potential bias. Some confounders were not measured specifically in the time windows most relevant to our opioid exposures of interest, which may result in residual confounding despite our adjustments. Last, we were unable to examine details of specific opioid drug, dose, and duration in relation to our outcomes.

We found that preconception opioid use was associated with lower fecundability, while use during early pregnancy was associated with pregnancy loss. Our study provides novel information about associations between opioid use and reproductive outcomes by assessing use throughout the critical preconception and early pregnancy periods among a group of healthy, non-opioid-dependent women. Negative consequences of opioid use for fertility and pregnancy are an underappreciated aspect of the ongoing opioid crisis. These outcomes represent an especially important public health concern given the high rates of opioid use among reproductive-age women. Our results highlight the importance of additional studies examining the types, duration, and dosage of opioids that could impact these outcomes. Given that opioids are often prescribed for pain after oocyte retrieval for *in vitro* fertilization, [23] the effect of these medications on outcomes after use of assisted reproductive technologies is another important area of study that should be explored. Meanwhile, for

women who may be pregnant or become pregnant, possible risks to fecundability and pregnancy viability may be relevant when determining approaches to pain management.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Sociodemographic characteristics of women in the EAGeR cohort with and without urine-measured preconception opioid exposure

Characteristics	Preconception opioid exposure (N=110)	No preconception opioid exposure (N=1108)
Age, years, mean ± SD	27.9 ± 4.9	28.8 ± 4.8
BMI, kg/m^2, mean ± SD	27.6 ± 7.9	26.2 ± 6.3
Race, N (%) white	102 (93)	1050 (95)
Education, N (%) with greater than high school	84 (76)	963 (87)
Income, N (%) ≥$75,000/year	59 (54)	574 (52)
Employed, N (%)	77 (72)	811 (76)
Physical activity level, N (%)		
Low	27 (25)	292 (26)
Moderate	47 (43)	449 (41)
High	36 (33)	366 (33)
Any smoking in past 12 months, N (%)	26 (24)	122 (11)
Any alcohol intake in past 12 months, N (%)	43 (40)	358 (33)
Marijuana use, N (%) any	7 (6)	53 (5)
Antidepressant use, N (%) any	37 (34)	170 (15)
Opioid use during and prior to last pregnancy, N (%) any	25 (23)	116 (11)
Intercourse frequency in past month, N (%)		
≥1 per week	80 (78)	766 (76)
<1 per week	22 (22)	240 (24)
Typical severity of abdominal cramping during menstrual period in past 12 months, N (%)		
None or mild	42 (40)	561 (53)
Moderate	37 (35)	373 (35)
Severe	27 (26)	125 (12)
Typical severity of lower back pain during menstrual period in past 12 months, N (%)		
None or mild	69 (65)	777 (74)
Moderate	25 (24)	214 (20)
Severe	12 (11)	66 (6)
Number of prior pregnancy losses, N (%)		
1	69 (63)	749 (68)
2	41 (37)	359 (32)
Number of prior live births, N (%) ≥1	65 (59)	631 (57)
Number of prior vaginal deliveries, N (%)		
0	62 (56)	659 (60)
1	34 (31)	293 (26)
≥2	14 (13)	150 (14)
Number of prior cesarean deliveries, N (%)		
0	98 (89)	945 (85)

Characteristics	Preconception opioid exposure (N=110)	No preconception opioid exposure (N=1108)
≥1	12 (11)	163 (15)
Time since last pregnancy resolution, weeks (median (25^{th}, 75^{th} percentile))	16.3 (6.6, 36.6)	15.4 (8.0, 37.3)
Last pregnancy resulted in non-live outcome, N (%)	106 (97)	1016 (93)
Aspirin treatment arm, N (%)	110 (49)	505 (50)
Withdrew from study, N (%)	21 (19)	116 (11)
Study site, N (%)		
Pennsylvania	7 (6)	68 (6)
New York	7 (6)	69 (6)
Utah	95 (86)	900 (81)
Colorado	1 (1)	71 (6)

Table 2.

Time to pregnancy by urine-measured[a] opioid use among all women enrolled in the EAGeR cohort

Opioid use exposure	N, exposed and unexposed[b]	N (%), pregnancies	Unadjusted FOR (95% CI)[c]	Adjusted FOR (95% CI)[d]
Overall	1228	797 (65)		
At baseline				
Negative	1124	742 (66)	Reference	Reference
Positive	87	43 (49)	0.70 (0.50, 0.98)	0.71 (0.50, 1.0)
Any time before conception				
Negative	1108	732 (66)	Reference	Reference
Positive	110	58 (53)	0.72 (0.54, 0.96)	0.75 (0.55, 1.0)

FOR, fecundability odds ratio; CI, confidence interval.

[a]Includes oxycodone, hydrocodone, noroxycodone, oxymorphone, codeine, dihydrocodeine, hydromorphone, morphine, desomorphine, heroin, levorphanol, thebaine, tramadol, and fentanyl.

[b]Numbers include participants with measured data. Multiple imputation was used to account for missing exposure and covariate information, thus all 1228 participants were included in analyses of FOR.

[c]From discrete time Cox proportional hazard models accounting for right censoring and left truncation.

[d]Adjusted for age, race, body mass index, education level, physical activity, smoking frequency, alcohol use frequency, urine-measured or self-reported marijuana use, urine-measured or self-reported antidepressant use, gynecological indication for opioid use, severity of abdominal cramping and lower backache during menstrual periods, time since a woman's last pregnancy, and number of prior pregnancy losses.

Table 3.

Live birth incidence by urine-measured[a] opioid use among women with complete follow-up in the EAGeR cohort, weighted to account for loss to follow-up

Opioid use exposure	N, exposed and unexposed[b]	N (%), live births	Unadjusted RR (95% CI)[c]	Adjusted RR (95% CI)[d]
Overall	1088	597 (55)		
At baseline				
Negative	1008	557 (55)	Reference	Reference
Positive	66	32 (49)	0.82 (0.65, 1.0)	0.87 (0.63, 1.2)
Any time before conception				
Negative	992	551 (56)	Reference	Reference
Positive	89	42 (47)	0.82 (0.66, 1.0)	0.85 (0.63, 1.2)

RR, risk ratio; CI, confidence interval.

[a]Includes oxycodone, hydrocodone, noroxycodone, oxymorphone, codeine, dihydrocodeine, hydromorphone, morphine, desomorphine, heroin, levorphanol, thebaine, tramadol, and fentanyl.

[b]Numbers include participants with measured data. Multiple imputation was used to account for missing exposure and covariate information, thus all 1088 participants with complete follow-up were included in analyses of RR.

[c]From Poisson regression models.

[d]Adjusted for age, race, body mass index, education level, physical activity, smoking frequency, alcohol use frequency, urine-measured or self-reported marijuana use, urine-measured or self-reported antidepressant use, gynecological indication for opioid use, severity of abdominal cramping and lower backache during menstrual periods, time since a woman's last pregnancy, and number of prior pregnancy losses.

Table 4.

Pregnancy loss incidence by urine-measured[a] opioid use among women in the EAGeR cohort who became pregnant

Opioid use exposure	N, exposed and unexposed[b]	N (%), losses	Unadjusted RR (95% CI)[c]	Adjusted RR (95% CI)[d]
Overall	785	188 (24)		
At baseline				
Negative	731	174 (24)	Reference	Reference
Positive	42	10 (24)	0.88 (0.55, 1.4)	0.96 (0.55, 1.7)
Any time before conception				
Negative	721	170 (24)	Reference	Reference
Positive	57	15 (26)	1.11 (0.76, 1.6)	1.16 (0.72, 1.9)
Last preconception cycle				
Negative	719	169 (24)	Reference	Reference
Positive	33	11 (33)	1.29 (0.84, 2.0)	1.5 (0.85, 2.6)
Week 4 of pregnancy[g]				
Negative	720	152 (21)	Reference	Reference
Positive	20	8 (40)	2.2 (1.3, 3.5)	2.09 (1.1, 4.1)
During first 8 weeks of pregnancy[g]				
Negative	653	82 (13)	Reference	Reference
Positive	33	9 (27)	2.4 (1.4, 4.0)	2.5 (1.3, 5.0)

RR, risk ratio; CI, confidence interval.

[a] Includes oxycodone, hydrocodone, noroxycodone, oxymorphone, codeine, dihydrocodeine, hydromorphone, morphine, desomorphine, heroin, levorphanol, thebaine, tramadol, and fentanyl.

[b] Restricted to women who became pregnant. Numbers include participants with measured data. Multiple imputation was used to account for missing exposure and covariate information, thus all 785 participants with complete follow-up were included in analyses of RR.

[c] From Poisson regression models restricted to women who became pregnant. Inverse probability weights were used to account for possible selection bias resulting from this restriction.

[d] Adjusted for age, race, body mass index, education level, physical activity, smoking frequency, alcohol use frequency, urine-measured marijuana use and antidepressant use at baseline, past opioid use prior to or during a woman's last pregnancy, gynecological indication for opioid use, severity of abdominal cramping and lower backache during menstrual periods, time since a woman's last pregnancy, and number of prior pregnancy losses.

[e] Restricted to women who had a pregnancy lasting at least 4 weeks. Inverse probability weights were used to account for possible selection bias resulting from this restriction. Multivariable model is adjusted for preconception opioid use and abdominal pain and cramping in the two weeks prior to opioid measurement.

[f] Restricted to women who had a pregnancy lasting at least 8 weeks. Inverse probability weights were used to account for possible selection bias resulting from this restriction. Multivariable model is adjusted for preconception opioid use and abdominal pain and cramping in the two weeks prior to opioid measurement.