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Differences in the association between oral glucocorticoids and risk of preterm birth by data source: Reconciling the results

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Abstract

Objective: To investigate causes of discrepancies in the association between early pregnancy oral glucocorticoids (OCS) use and preterm birth (PTB) risk among women with rheumatoid arthritis (RA) in health care utilization [California Medicaid (Medi-Cal)] and prospective cohort (MotherToBaby Pregnancy Studies) data.

Methods: Separately, we estimated risk ratios (RR) between OCS exposure before gestational day 140 and PTB risk in Medi-Cal (2007–2013; n=844) and MotherToBaby (2003–2014; n=528) data. We explored differences in socio-economic status, OCS dose distribution, exposure misclassification, and confounding by RA severity across the data sources.

Results: PTB risk in women without OCS's was 17.3% in Medi-Cal and was 9.7% in MotherToBaby. There was no association between OCS and PTB in Medi-Cal (adjusted (a)RR: 1.00 (95% confidence interval (CI): 0.71, 1.42)), and a 1.85-fold (95% CI: 1.20, 2.84) increased PTB risk in MotherToBaby. When restricting each sample to women with a high school degree or less, PTB risk following no OCS exposure was 15.9% in Medi-Cal and 16.7% in MotherToBaby; aRR's were 1.16 (95% CI: 0.74, 1.80) in Medi-Cal and 0.81 (95% CI: 0.25, 2.64) in MotherToBaby. Cumulative OCS dose was higher in MotherToBaby (median: 684 mg) than Medi-Cal (median: 300 mg). OCS dose 300 mg was not associated with increased PTB risk. Exposure misclassification and confounding by RA severity were unlikely explanations of differences.

Discussion: Higher baseline PTB risk and lower OCS dose distribution in Medi-Cal may explain the discrepancies. Studies are needed to understand the effects of autoimmune disease severity and under-treatment on PTB risk in low-income populations.

Keywords

epidemiology; glucocorticoids; pregnancy; preterm birth; rheumatoid arthritis

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Introduction

Oral glucocorticoids (OCSs) may be used to manage flares/exacerbations or for chronic management of autoimmune diseases including rheumatoid arthritis (RA) during pregnancy.[1–6] Prospective cohort and health care utilization database studies have reported an increased risk of preterm birth (PTB) following OCS use in women with RA and other autoimmune diseases.[7–12]

The use of healthcare utilization databases to study medication safety during pregnancy is becoming increasingly common.[13] These pre-existing data sources can increase feasibility and efficiency of studying relatively rare exposure and perinatal outcomes while reducing costs compared with primary data collection.[13,14] However, these data are not collected for research, and misclassification, unmeasured confounding, and restriction to patients with public or employer-based insurance are concerns.[13,14] Well-designed prospective studies can collect detailed information, but participants may differ from the target population of interest. It is unclear whether these differences related to internal validity (i.e., bias) and external validity (i.e., the extent to which results from the study sample hold for the population of interest) limit comparisons of medication safety in pregnancy between the two types of data sources.

When studies of the same perinatal medication safety question are available from healthcare utilization and prospective cohort data, results should be purposely compared, as threats to internal and external validity across data sources make clinical interpretation problematic. Therefore, we aimed to examine the same research question using both types of data, namely to what extent does OCS use early in pregnancy affect the risk of PTB among women with RA? We studied the association in a prospective cohort of women from the MotherToBaby Pregnancy Studies and among women enrolled in the California Medicaid Program (known as Medi-Cal). We conceptualized the target population, i.e., the population of interest, for our study question as pregnant women in the United States who have RA, recognizing that our study samples were not drawn at random from this population. Instead, women enrolled in MotherToBaby primarily had higher socio-economic status (SES), whereas women enrolled in Medi-Cal had lower SES because it is the joint state and US federal health insurance program for low-income individuals.

We found differing results from the two studies and explored potential reasons for the differences. To assess whether issues with internal validity could explain the discrepant results, we explored the potential for exposure misclassification (i.e., incorrectly classifying whether or not women used OCS) and residual confounding by RA severity within the two studies. We did not investigate outcome misclassification as an explanation for the observed differences because both studies used similar approaches to estimate gestational age at delivery, i.e., primarily ultrasound measurements with correction for discrepancies. Furthermore, we did not evaluate selection bias due to pregnancy loss because OCS use is not expected to increase the risk of pregnancy loss.[15] To assess whether issues related to external validity could explain the discrepant results, we explored differences in SES, a potential effect modifier, and cumulative OCS dose distribution across the study samples.

Patients and Methods

We previously conducted related studies on OCS exposure during pregnancy and risk of PTB in both data sources, and the methods have been described in detail.[12,16] We aimed to make the current analyses as similar as possible given differences in data elements across the data sources. To simplify the current analyses and comparisons across studies, we focused on any OCS exposure during the first half of pregnancy. Furthermore, we limited the study populations to women with RA to reduce potential confounding by underlying disease. The Medi-Cal study was approved by the Committee for the Protection of Human Subjects, California Health and Human Services Agency and was determined exempt by the University of California San Diego Human Research Protections Program. A data use agreement was in place with the California Department of Health Care Services. Counts of <16 were suppressed. The MotherToBaby Pregnancy Studies were approved by the University of California, San Diego Institutional Review Board and the current analysis was exempt. Informed consent was obtained in the MotherToBaby Pregnancy Studies.

We used 2007–2013 Medi-Cal enrollment and outpatient, inpatient, and pharmacy claims data linked to birth certificate and hospital discharge data for women with a live birth, continuous Medi-Cal enrollment during pregnancy, and an inpatient or outpatient ICD-9 International Classification of Diseases, Ninth Revision diagnosis code for RA (714.x) during pregnancy (n=844). Women were classified as exposed to OCS if they had a pharmacy dispensing for any OCS between the LMP date and gestational day 139 (ie, 20 gestational weeks). Gestational age at delivery was primarily determined from the birth certificate obstetric estimate.[17] Last menstrual period (LMP) date was calculated from the birth certificate by subtracting the obstetric estimate of gestational age at delivery from the delivery date. Alternatively the birth certificate LMP estimate of gestational age at delivery was used when the obstetric estimate was unavailable,[17] though most women (84%) meeting the inclusion criteria had the obstetric estimate available.

MotherToBaby Pregnancy Studies conduct prospective cohorts of several diseases and exposures during pregnancy, enrolling pregnant women in the United States and Canada.[18,19] MotherToBaby participants were self-referred, referred by healthcare providers, or referred by MotherToBaby, a free service of the Organization of Teratology Information Specialists providing evidence-based information on exposures in pregnancy and lactation.[18,19] We included pregnant women with a livebirth or stillbirth who enrolled in MotherToBaby Autoimmune Diseases in Pregnancy Study (2003–2014) before gestational day 140 and reported having RA and excluded women missing information on RA-related medications including OCS (n=9).[12] There were a total of 528 women who met the eligibility criteria, including one with stillbirth. Trained study staff conducted up to four semi-structured telephone interviews with participants: at enrollment (before gestational week 20), approximately 24 and 32 weeks' gestation, and after delivery. Interviewers collected data on demographics, reproductive history, pre-pregnancy weight and height, comorbidities, smoking, and pregnancy outcomes.[20] At study enrollment, interviewers used an open-ended prompt to obtain information on medication use such as 'Have you taken any over-the-counter medications since your last menstrual period, for example, Tylenol® or Tums®?' Women who reported having a specific illness or disease were asked if they took

any medication for that condition, e.g. rheumatoid arthritis. For all medications reported, women were queried about dose and dates of use. During follow-up interviews, women were queried about medication use since their most recent interview and whether they were using previously reported medications.[20] Interviewers administered self-assessment questionnaires to measure RA severity including the Health Assessment Questionnaire Disability Index (HAQ; a validated measure of functional status in patients with RA; possible range from 0=no disability to 3=completely disabled),[21,22] pain score (pain severity rating in the past week; possible range from 0=no pain to 100=severe pain), and patient's global score (overall health rating; possible range from 0=very well to 100=very poor). Gestational age at delivery was estimated from the LMP date with adjustment for discrepant ultrasound measurements. Women were classified as exposed if they reported any OCS use between the LMP date and gestational day 139.

PTB was classified as delivery at <37 gestational weeks, i.e., <259 days. We assessed the association between any OCS exposure and PTB using Poisson regression with robust variance to estimate risk ratios (RR) and 95% confidence intervals (CI).[23] We also estimated risk differences (RD) and 95% CI using linear regression with robust variance. We identified covariates a priori that we hypothesized to be potential confounders. We adjusted estimates for a common set of covariates available in both data sources and additional covariates unique to both data sources to further address confounding. The modeling approaches (ie, functional form, categorization cut points) are described in the Supplementary Table 1. The common covariates were LMP year (<2010, 2010; cut point about halfway through the years of data for Medi-Cal), maternal age, race/ethnicity, maternal education, multiple gestation, pre-pregnancy body mass index, primiparity, hypertension, autoimmune comorbidities, and, as proxies of RA severity, nonsteroidal anti-inflammatory drugs and disease modifying antirheumatic drugs (DMARDs), including conventional and biologic therapies, between the LMP and day 139. In Medi-Cal, we also adjusted for being in the disability category for Medicaid eligibility, general markers of comorbidity (any hospitalizations, number of outpatient and emergency department visits)[24] and disease severity proxies between LMP and day 139 (number of outpatient visits with RA diagnosis, inflammatory marker and rheumatoid factor labs).[25] In MotherToBaby, we also adjusted for socioeconomic status (SES) using Hollingshead categories of maternal and paternal education[26] to further account for confounding by socio-economic status, and HAQ, pain, and global scores at the time of enrollment to adjust for RA severity.

In post-hoc analyses, we explored the four factors that we expected to differ between the two data sources as potential explanations of discrepant results, discussed below.

1. SES. Pregnant women enrolled in Medi-Cal meet low income thresholds, whereas MotherToBaby participants primarily have higher SES.[12] We used education as an SES proxy because it was measured in both studies. To make the two populations more similar, we restricted to high school degree or less education in both data sources. We present characteristics for the restricted and full study populations and estimated the associations in the restricted population.

2. Dose. Higher OCS doses have been associated with higher PTB risk in both data sources.[12,15] Therefore, differences in typical OCS dose across studies could

contribute to differences in the association between *any* OCS use and PTB. We assessed the median total cumulative OCS dose (prednisone equivalent dose)[27] between the LMP and gestational day 139. Then we assessed the association between high and low OCS cumulative dose versus no OCS exposure between the LMP and day 139 and PTB, using the lower of two median doses as the exposure cut point.

3. Exposure misclassification. We anticipated greater exposure misclassification in Medi-Cal than MotherToBaby because we could not confirm OCS use as assumed from dispensing data. Previously using MotherToBaby data, we compared prednisone (the most common OCS during pregnancy)[28,29] use in medical records versus maternal report during pregnancy in women with RA and found a sensitivity of 56% (95 % CI: 47%, 64%) and specificity of 89% (95% CI: 82%, 94%).[20] We expect a similar degree or less exposure misclassification in claims data versus the medical records in our previous study. This because the claims were comprised of pharmacy dispensing data, whereas the data from the medical records were from medication orders, not fills, and from active medication lists and physicians' notes, which generally required a health care visit for updates/reconciliation. We conducted a probabilistic bias analysis of exposure misclassification simultaneously adjusting for measured covariates using the approach and macro described by Fox et al[30] to assess the degree of misclassification needed in Medi-Cal to produce the same adjusted RR in MotherToBaby (details in Supplementary Methods).

4. Residual confounding. Given that MotherToBaby collected validated self-reported measures of RA severity[21,22] and we had to rely on proxies of disease severity in Medi-Cal, we were particularly concerned about confounding by RA severity in the Medi-Cal analysis. We anticipate that residual confounding by RA severity would lead to upward bias as greater disease severity is associated with an increased risk of PTB[19] and greater disease severity is associated with OCS use (as observed in MotherToBaby in Table 1 below). We compared fully-adjusted models to those without severity adjustment. Also, we conducted a bias analysis for unmeasured confounding by RA severity in Medi-Cal by adjusting the exposure-misclassification bias analysis point estimates between OCS exposure and PTB for an unmeasured confounder using the array approach described by Schneeweiss[31] and implemented with the episensr package in R statistical software (details in Supplementary Methods).[32] All other analyses were conducted using SAS statistical software (version 9.4).

Results

Primary analysis

Before gestational day 140, 22.4% of women in Medi-Cal and 49.1% of women in MotherToBaby had OCS exposure (Table 1). DMARD use before gestational day 140, including biologic therapies, was far less common in Medi-Cal (17.5% DMARD; 6.5% biologic DMARD) than MotherToBaby (79.7% DMARD; 67.4% biologic DMARD).

DMARDs were more common among OCS exposed versus unexposed in Medi-Cal (38.6% versus 11.5%) but not in MotherToBaby (80.3% versus 79.2%). Proxies and measures of disease severity were more common among OCS exposed versus unexposed women in both studies. In Medi-Cal, 68.4% of women had high school degree equivalent or less education, whereas only 9.5% were in this category in MotherToBaby.

PTB risk in women without OCSs was 17.3% in Medi-Cal and 9.7% in MotherToBaby (Tables 2 and 3), whereas the PTB risk in women with OCSs were more similar across data sources (19.1% in Medi-Cal and 21.6% in MotherToBaby). Therefore, no association existed between OCS exposure and PTB in Medi-Cal (adjusted risk ratio (aRR): 1.00 (95% CI: 0.71, 1.42), adjusted risk difference (aRD): 0.0 (−95% CI: −6.3, 6.4)), and there was an adjusted 1.85-fold (95% CI: 1.20, 2.84) increased risk and an 8.3% (95% CI: 2.6%, 14.0%) absolute increase in the risk for PTB in MotherToBaby.

Restriction

When restricting Medi-Cal to lower education, characteristics were similar to the full population with the exception of an increase in the proportion of women who were Hispanic from 64.3% to 74.0% (Table 4). Upon restriction in MotherToBaby, the proportion of non-Hispanic White women decreased (79.0% to 52.0%), overweight/obese women increased (38.6% to 48.0%, and RA severity increased (e.g., median HAQ score increased from 0.3 to 0.6 with restriction). Upon restriction, PTB risk among women with no OCS exposure during the first 139 days decreased slightly to 15.9% in Medi-Cal and increased to 16.7% in MotherToBaby. The adjusted association between OCS exposure and PTB did not change materially in Medi-Cal (aRR: 1.16 (95% CI: 0.74, 1.80)) and it decreased in MotherToBaby although the estimate was imprecise (aRR: 0.81 (95% CI: 0.25, 2.64)).

Dose and risk

Total cumulative OCS dose during the first half of pregnancy was higher in MotherToBaby (median: 684 mg prednisone equivalent dose) than Medi-Cal (median: 300 mg prednisone equivalent dose). OCS dose ≤ 300 mg prednisone equivalent dose was not associated with increased PTB risk in either study (Tables 2 and 3). Although absolute risks for PTB were similarly high across both studies for OCS dose >300 mg (25.0% for Medi-Cal; 26.7% for MotherToBaby), the aRRs differed across the two studies (Medi-Cal aRR 1.23 (95% CI: 0.91, 1.68); MotherToBaby aRR: 2.22 (95% CI: 1.43, 3.45)) as did the aRDs (Medi-Cal aRD −3.7% (−8.9%, 1.5%); MotherToBaby aRD: 13.0% (6.1%, 19.9%)).

Exposure misclassification adjustment

Assuming non-differential misclassification (i.e., OCS misclassification unrelated to PTB status), sensitivity=60%, and specificity=85%, the exposure misclassification bias analysis aOR was 1.40 (0.89, 2.28) (Supplementary Table 2). Assuming differential misclassification (i.e., OCS misclassification differing by PTB status) with sensitivity=60%, specificity=95% for women with PTB, and specificity=85% for women without PTB yielded a bias-adjusted aOR of 3.05 (1.71, 6.62) (Supplemental Table 3). With sensitivity=60%, specificity=85% for women with PTB, and specificity=95% for women without PTB, the bias-adjusted aOR of 0.52 (0.26, 0.92).

Severity adjustment

Compared with adjusting for all covariates, not adjusting for disease severity increased the RR by 11% MotherToBaby (RR: 2.05 (95% CI: 1.32, 3.17)). Not adjusting for severity proxies did not change the Medi-Cal results materially. The bias analysis for exposure misclassification and unmeasured confounding by RA severity in Medi-Cal indicated a reduced point estimate after adjusting for the unmeasured confounder (e.g., exposure misclassification bias analysis aOR=1.40, exposure misclassification and unmeasured confounding bias analysis RR=1.18; Supplementary Tables 2 and 3).

Discussion

We observed no association between OCS use during the first half of pregnancy and PTB among women with RA when using Medi-Cal data. However, a similar analytic approach with prospective cohort data yielded an 8% absolute increase in the risk for PTB and nearly a 2-fold increased risk for PTB following OCS exposure during the first half of pregnancy. Based on post hoc bias analyses, difference in the results across studies seemed unlikely related to threats to internal validity. Instead, differences in the study samples related to SES and OCS dose distribution may have contributed to the discrepancy in the associations across studies.

PTB risk following OCS exposure was similar in both studies; the disparity in results from the full populations originates in the reference groups. Women in Medi-Cal were low income and primarily Hispanic. Furthermore, most women were overweight/obese, and few used DMARDs, several of which are recommended to control disease activity and reduce the risks of flares during pregnancy (e.g., hydroxychloroquine),[33,34] likely resulting in increased disease activity. These factors may have contributed to the high observed baseline risk of PTB. Women in MotherToBaby self-selected into the study, which may be a proxy for health-seeking behaviors protective for PTB, had high SES, and were primarily non-Hispanic White. Most women were normal-weight/underweight, had relatively low disease severity, and used DMARDs including biologic therapies (which were not associated with an increased risk of PTB in these studies[12,15]), resulting in lower baseline PTB risk compared with Medi-Cal. Among RA patients in the general population, major disparities in access to DMARDs related to race and socio-economic status have been described, with Medicaid patients being far less likely to receive DMARDs than patients with private insurance.[35,36] Therefore, SES may influence the baseline risk for PTB among pregnant women with RA through a variety of pathways, e.g., decreased access to DMARDs resulting in increased RA severity.

OCS exposure was not associated with PTB when restricting to women with lower education in either study, although the point estimate was imprecise for MotherToBaby as <10% had lower education. After restriction to women with lower education, the impact of OCS exposure on the development of PTB may have been negligible given high baseline risk for PTB (approximately 16% in both studies). Increased RA severity due to less DMARD use and other factors, e.g., inadequate prenatal care, environmental pollution, or experiences of racism,[37–40] may have been more impactful contributors to PTB than OCSs in a population with lower SES. Therefore, SES appears to be an important effect modifier of the association

between OCS use during pregnancy and PTB and should be considered when generalizing estimates to the target population or transporting estimates to other populations.[41]

The median total cumulative dose of OCSs during the first half of pregnancy in Medi-Cal was less than half that observed in MotherToBaby. Furthermore, lower OCS doses were not associated with an increased PTB risk in either population. Therefore, the lower distribution of cumulative OCS dose in Medi-Cal may have contributed to the null association observed between OCS and PTB in Medi-Cal. Differences in typical OCS regimes with respect to dose across the study samples may have contributed to the discrepancy across the studies.

We assumed that OCS exposure was captured with higher accuracy in MotherToBaby than Medi-Cal given the careful collection of medication use information via semi-structured interviews at multiple time points during pregnancy in MotherToBaby versus the reliance on pharmacy dispensing data in Medi-Cal. Using estimates from our validation study of OCS exposure during pregnancy,[20] correcting for OCS misclassification unrelated to PTB status in Medi-Cal led to point estimates that were weaker than those observed in MotherToBaby. Correcting for OCS misclassification related to PTB status in Medi-Cal led to point estimates that were stronger than in MotherToBaby when accuracy was higher in women with PTB than without PTB. However, plausibility is low given that exposure was classified during the first half of pregnancy, well before PTB occurred. Therefore, misclassified OCS status in Medi-Cal seems unlikely to have explained the observed discrepancy across the studies.

We assumed that we were able to more fully adjust for RA severity in MotherToBaby given validated measures of RA severity[21,22] versus proxies of severity in Medi-Cal. Quantitative bias analysis for residual confounding by disease severity following correction for exposure misclassification in Medi-Cal resulted in a weakened association between OCS and PTB that was lower than the MotherToBaby point estimate. Therefore, residual confounding by RA severity in Medi-Cal was not a likely explanation for the observed differences across the studies.

A limitation of our study is the small number of women with lower education in MotherToBaby resulting in imprecise estimates when exploring the impact of making the study populations more similar with respect to SES. Furthermore, although we aimed to create more comparable study populations by restricting to women with the same education level, we acknowledge that education level is a proxy of SES and there are socioeconomic and other sources of variability across the two restricted populations (e.g., health behaviors). All of the women in the Medi-Cal study met low-income eligibility criteria, whereas some women with a high school education or less in MotherToBaby were still classified as having higher SES according to Hollingshead's categories. Medicaid status was not available in MotherToBaby. Furthermore, we had to rely on diagnostic codes to classify RA in Medi-Cal, which may have resulted in the inclusion of some women without RA.

Our study intentionally analyzed the same medication safety question in prospective cohort data and health care utilization data and investigated potential reasons for discrepant answers. We used a similar analytic approach across the data sources, and the data sources

had complementary strengths which allowed us to investigate several reasons for differing results. Medi-Cal allowed us to investigate the association of interest in a low-income population without selection of volunteers. MotherToBaby had careful ascertainment of OCS use with maternal report and medical record confirmation and self-reported validated measures of disease severity.

Results of individual studies of medication safety during pregnancy are often at odds with each other. Discrepant results can make counseling on medication safety complex for providers and decision making fraught for patients. When discrepant results arise, ideally investigators could quantitatively explore threats to internal validity including exposure misclassification, outcome misclassification, confounding, and selection bias, as well as external validity issues including differences in study populations related to baseline risks, the distribution of effect modifiers, and treatment regimens, including daily and/or cumulative dose, as possible explanations. In our comparison, differences in results across the data sources may be due to the underlying risk of the outcome in the referent groups of each study. We also observed differences in the distribution of OCS dose which may have contributed to differences in the association between OCS modeled as a binary yes/no variable and PTB.[42] However, we could not attribute the differences in results to expected biases in Medi-Cal data (ie, exposure misclassification, confounding). Our findings underscore the need 1) for authors to describe and contextualize study samples, assess medication dose, and present stratum-specific results for potential effect modifiers, 2) for readers to consider characteristics of the study sample, baseline risks, and medication dose distribution when comparing discrepant answers to the same perinatal medication safety question.

Given the high baseline risk for PTB among Medi-Cal enrollees with RA and replicated among women with a high school education or less in MotherToBaby, and also in enrollees with asthma, systemic lupus erythematosus, and inflammatory bowel disease as described previously,[16] studies are needed to understand the effects of autoimmune disease severity and undertreatment of autoimmune diseases on PTB risk before and during pregnancy in low income populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

Conflicts of interests:

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Significance and Innovations

- Oral glucocorticoids exposure was not associated with PTB when restricting to women with lower education, but women with lower education had a high baseline risk of PTB of approximately 16%.

- Differing results from studies of perinatal medication safety, including studies of oral glucocorticoids use and PTB risk, may stem from differences in study populations, baseline risks, and dose distributions in addition to the typical sources of bias in observational studies (eg, exposure misclassification, outcome misclassification, confounding).

Table 1.

Characteristics among women in the Medi-Cal study and in the MotherToBaby (MTB) study overall and by exposure status.

Characteristic	Medi-Cal			MotherToBaby		
	Overall, n=844	No OCS, n=655	OCS, n=189	Overall, n=528	No OCS, n=269	OCS, n=259
LMP year 2010 or later, n (%)	556 (65.9)	430 (65.6)	126 (66.7)	219 (41.5)	124 (46.1)	95 (36.7)
Maternal age, median (IQ Range)	29.0 (9.0)	28 (9)	30 (9)	32 (6)	32 (6)	32 (6)
Race/Ethnicity						
White (Medi-Cal), Non-Hispanic white (MTB)	156 (18.5)	133 (20.3)	23 (12.2)	417 (79.0)	221 (82.2)	196 (75.7)
Black	78 (9.2)	62 (9.5)	16 (8.5)	NA	NA	NA
Hispanic	543 (64.3)	411 (62.7)	132 (69.8)	NA	NA	NA
Other or Unknown	67 (7.9)	49 (7.5)	18 (9.5)	111 (21.0)	48 (17.8)	63 (24.3)
Maternal education, n (%)						
High school degree or equivalent or less	577 (68.4)	452 (69.0)	125 (66.1)	50 (9.5)	24 (7.9)	26 (10.0)
Less than high school degree	290 (34.4)	242 (37.0)	48 (25.4)	NA	NA	NA
High school degree or equivalent	287 (34.0)	210 (32.1)	77 (40.7)	NA	NA	NA
Some college, college degree or equivalent, or higher	267 (31.6)	203 (31.0)	64 (33.9)	478 (90.5)	245 (92.1)	233 (90.0)
Some college	NA	NA	NA	116 (22.0)	55 (20.4)	61 (23.6)
College degree or equivalent, or higher	NA	NA	NA	362 (68.6)	190 (70.6)	172 (66.4)
Disability as source of Medi-Cal eligibility	113 (13.4)	80 (12.2)	33 (17.5)	NA	NA	NA
Socioeconomic status[a], median (IQ Range)	NA	NA	NA	2 (1)	2 (1)	2 (1)
Gestational age at enrollment, median (IQ Range)	NA	NA	NA	11 (7)	11 (7)	11 (8.)
Multiple gestation, n (%)	-	-	-	23 (4.4)	8 (3.0)	15 (5.8)
Pre-pregnancy body mass index, n (%)						
Underweight to normal weight	317 (37.6)	247 (37.7)	70 (37.0)	324 (61.4)	156 (58.0)	168 (64.9)
Overweight	253 (30.0)	200 (30.5)	53 (28.0)	114 (21.6)	55 (20.4)	59 (22.8)
Obese	274 (32.5)	208 (31.8)	66 (34.9)	90 (17.0)	58 (21.6)	32 (12.4)
Primiparous, n (%)	198 (23.5)	167 (25.5)	31 (16.4)	249 (47.2)	126 (46.8)	123 (47.5)
Autoimmune comorbidities[b], n (%)	83 (9.8)	53 (8.1)	30 (15.9)	29 (5.5)	12 (4.5)	17 (6.6)
Hypertension[c] (Medi-Cal)/Pre-pregnancy hypertension (MTB), n (%)	33. (3.9)	21 (3.2)	-	37 (7.0)	18 (6.7)	19 (7.3)
DMARD[c], n (%)	148 (17.5)	75 (11.5)	73 (38.6)	421 (79.7)	213 (79.2)	208 (80.3)

Characteristic	Medi-Cal			MotherToBaby		
	Overall, n=844	No OCS, n=655	OCS, n=189	Overall, n=528	No OCS, n=269	OCS, n=259
NSAID[c,d], n (%)	171 (20.3)	100 (15.3)	71 (37.6)	191 (36.2)	85 (31.6)	106 (40.9)
Number of outpatient visits[c], n (%)						
None	292 (34.6)	227 (34.7)	65 (34.4)	NA	NA	NA
1 to 5	330 (39.1)	265 (40.5)	65 (34.4)	NA	NA	NA
6	222 (26.3)	163 (24.9)	59 (31.2)	NA	NA	NA
Number of emergency department visits[c], n (%)						
None	510 (60.4)	408 (62.3)	102 (54.0)	NA	NA	NA
1	131 (15.5)	101 (15.4)	30 (15.9)	NA	NA	NA
2	203 (24.1)	146 (22.3)	57 (30.2)	NA	NA	NA
1 Inpatient admission[c]	26 (3.1)	-	-	NA	NA	NA
Number of outpatient visits with RA diagnosis[c], n (%)						
None	592 (70.1)	475 (72.5)	117 (61.9)	NA	NA	NA
1	157 (18.6)	121 (18.5)	36 (19.1)	NA	NA	NA
2	95 (11.3)	59 (9.0)	36 (19.0)	NA	NA	NA
Inflammatory marker lab[c], n (%)	128 (15.1)	82 (12.5)	46 (24.3)	NA	NA	NA
Rheumatoid factor lab[c], n (%)	82 (9.7)	65 (9.9)	17 (9.0)	NA	NA	NA
HAQ at enrollment[e], median (IQ range)	NA	NA	NA	0.3 (0.9)	0.1 (0.6)	0.5 (1.0)
Pain score at enrollment[f], median (IQ range)	NA	NA	NA	20.0 (45)	10 (25)	25 (50)
Global score at enrollment[g], median (IQ range)	NA	NA	NA	15.0 (35)	10 (30)	25 (45)
OCS cumulative dose[c,h] median (IQ range)	300 (420)	0 (0)	300 (420)	684 (645)	0	684 (645)

Abbreviations: DMARD, disease modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; IQ, Interquartile; LMP, last menstrual period; NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug; OCS, oral corticosteroid; RA, rheumatoid arthritis.

-Counts of <16 were suppressed for Medi-Cal.

[a] 8 women missing socio-economic status. Hollingshead categories (possible range from highest = 1 to lowest = 5).

[b] Inflammatory bowel disease, lupus, or ankylosing spondylitis for Medi-Cal; Inflammatory bowel disease, lupus, or ankylosing spondylitis for MotherToBaby.

[c] Between LMP and gestational day 139.

[d]Prescription NSAID only for Medi-Cal.

[e]Health Assessment Questionnaire (possible range from 0=no disability to 3=completely disabled).

[f]Pain score (possible range from 0=no pain to 100=severe pain).

[g]Global score (possible range from 0=very well to 100=very poor).

[h]Among women with any OCS exposure between LMP and gestational day 139; prednisone equivalent dose.

Table 2.

Oral corticosteroid (OCS) exposure between last menstrual period (LMP) and day 139 and risk of preterm birth among women in the Medi-Cal study.

Exposure group	N	% PTB	Crude RR & 95% CI	Adjusted RR & 95% CI[a]	Crude RD & 95% CI	Adjusted RD & 95% CI[a]
All Women	844					
OCS	189	19.1	1.10 (0.78, 1.56)	1.00 (0.71, 1.42)	1.8 (−4.6, 8.2)	0.0 (−6.3, 6.4)
>300 mg cumulative dose[b]	84	25.0	1.36 (1.01, 1.85)	1.23 (0.91, 1.68)	6.2 (−0.7, 13.0)	4.2 (−2.3, 10.7)
300 mg cumulative dose[b]	105	-	-	0.81 (0.59, 1.12)	-	−3.7 (−8.9, 1.5)
No OCS	655	17.3	Reference	Reference	Reference	Reference
High School Degree Equivalent or Less Education	565					
OCS	125	20.8	1.31 (0.86, 1.98)	1.16 (0.74, 1.80)[e]	4.9 (−3.2, 13.0)	2.9 (−5.2, 11.0)
No OCS	440	15.9	Reference	Reference	Reference	Reference

Abbreviations: CI, confidence interval; PTB, preterm birth; RR, risk ratio.

[a] Adjusted for: LMP year (<2010, 2010), maternal age, race/ethnicity, maternal education, disability as source of Medi-Cal eligibility, multiple gestation, pre-pregnancy body mass index category, nulliparity, inflammatory bowel disease or lupus (yes, no), and hypertension, disease modifying antirheumatic drug, prescription nonsteroidal anti-inflammatory drug, any inpatient admission, any inflammatory marker labs, any rheumatoid factor labs, number of outpatient visits, emergency department visits, and outpatient visits with a rheumatoid arthritis diagnosis between LMP and gestational day 139.

[b] Prednisone equivalent dose.

Table 3.

Oral corticosteroid (OCS) exposure between last menstrual period (LMP) and day 139 and risk of preterm birth among women in the MotherToBaby study.

Exposure Group	N	% PTB	Crude RR & 95% CI	Adjusted RR & 95% CI [a]	Crude RD & 95% CI	Adjusted RD & 95% CI [a]
All Women	528					
OCS	259	21.6	2.24 (1.45, 3.45)	1.85 (1.20, 2.84) [c]	12.0 (5.8, 18.1)	8.3 (2.6, 14.0)
>300 mg cumulative dose [b]	180	26.7	2.74 (1.77, 4.25)	2.22 (1.43, 3.45)	16.9 (9.5, 24.2)	13.0 (6.1, 19.9)
300 mg cumulative dose [b]	75	9.3	1.06 (0.50, 2.25)	1.00 (0.49, 2.06)	5.9 (−7.0, 8.2)	−1.8 (−9.2, 5.5)
No OCS	269	9.7	Reference	Reference	Reference	Reference
High School Degree Equivalent or Less Education	50					
OCS	26	23.1	1.38 (0.44, 4.32)	0.81 (0.25, 2.64) [d]	6.4 (−15.6, 28.4)	−9.3 (−28.4, 9.7)
No OCS	24	16.7	Reference	Reference	Reference	Reference

Abbreviations: CI, confidence interval; PTB, preterm birth; RR, risk ratio.

[a] Adjusted for: LMP year (<2010, 2010), maternal age, non-Hispanic White race/ethnicity, maternal education, socioeconomic status (Hollingshead categories), multiple gestation, pre-pregnancy body mass index category, nulliparous, pre-pregnancy hypertension, inflammatory bowel disease, lupus, or ankylosing spondylitis (yes, no), disease modifying antirheumatic drug use between LMP and gestational day 139, nonsteroidal anti-inflammatory drug use between LMP and gestational day 139, and health assessment questionnaire score, pain score, and global score at time of enrollment.

[b] Prednisone equivalent dose.

[c] 8 women excluded because of missing socioeconomic status; results did not change materially when including all women without adjusting for socioeconomic status.

[d] 3 women excluded because of missing socioeconomic status; results did not change materially when including all women without adjusting for socioeconomic status.

Table 4.

Characteristics among those with a high school degree or equivalent or less education in the Medi-Cal study and in the MotherToBaby study.

Characteristic	Medi-Cal, n=565	MotherToBaby, n=50
LMP year 2010 or later, n (%)	367 (65.0)	17 (34.0)
Maternal age, median (IQ Range)	28 (9)	31 (7)
Race/Ethnicity		
White (Medi-Cal), Non-Hispanic white (MTB)	88 (15.6)	26 (52.0)
Black	33 (5.8)	NA
Hispanic	418 (74.0)	NA
Other or Unknown	26 (4.6)	24 (48.0)
Maternal education, n (%)		
High school degree or equivalent or less	565 (100)	50 (100)
Less than high school degree	282 (49.9)	NA
High school degree or equivalent	283 (50.1)	NA
Some college, college degree or equivalent, or higher	0 (0)	0 (0)
Disability as source of Medi-Cal eligibility	77 (13.6)	NA
Socioeconomic status[a], median (IQ Range)	NA	3 (1)
Gestational age at enrollment, median (IQ Range)	NA	11 (8)
Multiple gestation, n (%)	-	0 (0)
Pre-pregnancy body mass index, n (%)		
Underweight to normal weight	213 (37.7)	26 (52.0)
Overweight	165 (29.2)	14 (28.0)
Obese	187 (33.1)	10 (20.0)
Primiparous, n (%)	133 (23.5)	18 (36.0)
Autoimmune comorbidities[b], n (%)	54 (9.6)	3 (6.0)
Hypertension[c] (Medi-Cal)/Pre-pregnancy hypertension (MTB), n (%)	24 (4.2)	6 (12.0)
DMARD[c], n (%)	104 (18.4)	44 (88.0)
NSAID[c,d], n (%)	118 (20.9)	17 (34.0)
Number of outpatient visits[c], n (%)		
None	186 (32.9)	NA

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Characteristic	Medi-Cal, n=565	MotherToBaby, n=50
1 to 5	230 (40.7)	NA
6	149 (26.4)	NA
Number of emergency department visits [c], n (%)		
None	340 (60.2)	NA
1	93 (16.5)	NA
2	123 (23.4)	NA
1 Inpatient admission [c]	-	NA
Number of outpatient visits with RA diagnosis [c], n (%)		
None	392 (69.4)	NA
1	107 (18.9)	NA
2	66 (11.7)	NA
Inflammatory marker lab [c], n (%)	80 (14.2)	NA
Rheumatoid factor lab [c], n (%)	54 (9.6)	NA
HAQ at enrollment [e], median (IQ range)	NA	0.6 (1.1)
Pain score at enrollment [f], median (IQ range)	NA	28 (60)
Global score at enrollment [g], median (IQ range)	NA	23 (45)
OCS cumulative dose [c,h] median (IQ range)	300 (430)	695 (448)

Abbreviations: DMARD, disease modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; IQ, Interquartile; LMP, last menstrual period; NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug; OCS, oral corticosteroid; RA, rheumatoid arthritis.

-Counts of <16 were suppressed for Medi-Cal.

[a]8 women missing Socio-economic status. Hollingshead categories (possible range from highest = 1 to lowest = 5).

[b]Inflammatory bowel disease, lupus, or ankylosing spondylitis for Medi-Cal; Inflammatory bowel disease, lupus, or ankylosing spondylitis for MotherToBaby.

[c]Between LMP and gestational day 139.

[d]Prescription NSAID only for Medi-Cal.

[e]Health Assessment Questionnaire (possible range from 0=no disability to 3=completely disabled).

[f]Pain score (possible range from 0=no pain to 100=severe pain).

[g]Global score (possible range from 0=very well to 100=very poor).

[h]Among women with any OCS exposure between LMP and gestational day 139; prednisone equivalent dose.