Title

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Original article

Oral corticosteroid use during pregnancy and risk of preterm birth

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Abstract

Objective. To evaluate the associations between oral corticosteroid (OCS) dose early and late in pregnancy and preterm birth (PTB) among women with RA.

Methods. Pregnant women in the MotherToBaby Pregnancy Studies (2003–2014) with RA ($n = 528$) were included in the primary analysis. Information was collected by phone interview and from medical records. We estimated risk ratios (RR) for OCS dose trajectories and other disease-related medications before gestational day 140 and hazard ratios (HR) for time-varying exposures after gestational day 139.

Results. PTB risk was 15.5% overall. Compared with no OCS, PTB risk was increased in high (adjusted (a)RR: 4.77 (95% CI: 2.76, 8.26)) and medium (aRR: 1.81 (95% CI: 1.10, 2.97)) cumulative OCS dose trajectories during the first 139 gestational days. The low cumulative trajectory group was associated with an increased risk of PTB that was not statistically significant (aRR: 1.38 (95% CI: 0.79, 2.38)), and DMARDs were not associated with PTB (biologic DMARDs aHR: 1.08 (95% CI: 0.70, 1.66); non-biologic DMARDs aHR: 0.87 (95% CI: 0.55, 1.38)). OCS exposure to $\geqslant$10 mg of prednisone equivalent daily dose after gestational day 139 *vs* none was associated with increased PTB rate (aHR: 2.45 (95% CI: 1.32, 4.56)), whereas $<$10 mg was associated with a modestly increased rate of PTB that was not statistically significant (aHR: 1.18 (95% CI: 0.60, 2.30)).

Conclusion. Higher OCS doses *vs* no OCS use, both earlier and later in pregnancy, were associated with an increase in PTB among women with RA.

Key words: antirheumatic agents, autoimmune diseases, oral corticosteroids, pregnancy, preterm birth, rheumatoid arthritis

CLINICAL SCIENCE

Rheumatology key messages

- Higher OCS doses were associated with an increase in preterm birth among women with RA.
- Lower OCS doses were not clearly associated with preterm birth among women with RA.
- B-DMARD and NB-DMARD use were not associated with preterm birth among women with RA.

Introduction

For pregnant women with autoimmune diseases including RA, oral corticosteroids (OCSs) may be used to manage flares or for chronic management when other treatments are discontinued [1–4]. OCSs may be used during pregnancy to treat acute asthma exacerbations or severe persistent asthma [5, 6].

Systemic corticosteroid use has been associated with serious infection in pregnant women and serious and non-serious infection in individuals with autoimmune diseases, independent of other immunosuppressive medications, especially for doses of ~10 mg of prednisone equivalent per day and greater [7–11]. Intrauterine infection is believed to be a contributor to preterm birth (PTB) [12], and Schatz *et al.* proposed that immunosuppressive effects of OCSs could increase the risk of PTB through subclinical intra-amniotic infection [13]. Indeed, many studies have reported an increased risk of PTB or shorter gestational length following *any* OCS use during pregnancy among women with RA, systemic lupus erythematosus, IBD, asthma, and among all women regardless of autoimmune disease [13–29], yet there is limited information regarding the impact of dose and gestational timing of OCS use on PTB [23, 25]. We reported a reduction in gestational age at delivery associated with higher dose trajectories of prednisone (the most commonly used OCS

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during pregnancy) [30, 31] use during the first 32 gestational weeks as compared with lower dose trajectories among women with RA [32]. However, the association between OCS dose specifically during earlier and later gestational windows (i.e. during the first and second halves of pregnancy, separately) and the clinically relevant outcome of PTB has not been explored. Furthermore, there are limited data on comparisons between OCSs and other disease-related treatments and PTB risk adjusted for confounders [18, 20–22, 33, 34]. Finally, confounding by indication has been a concern for studies of OCS use and PTB as maternal autoimmune disease and control/activity are also associated with increased PTB risk [29, 35–43].

We assessed the association between OCS dose and other disease-related medication use and PTB in pregnant women with RA in the primary analysis, adjusting for disease severity at enrolment. Assuming OCS use impacts subclinical intrauterine infection, we hypothesized that higher doses of OCS later in pregnancy, as compared with no OCS use, would be associated with an increased rate of PTB, but that other disease-related medications would not be associated with PTB. We also evaluated associations between OCS use and PTB in smaller subcohorts of women with IBD and asthma in an exploratory analysis to determine whether any signals observed among women with RA would also be observed among women with other autoimmune conditions who may be treated with OCS.

Methods

The methods described below pertain to the primary analysis among women with RA. A further description for the IBD and asthma subcohorts can be found in Supplementary Methods, available at *Rheumatology* online.

Data sources

Data were from the MotherToBaby Pregnancy Studies [39, 44, 45], which 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. Participants from the United States and Canada 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 regarding exposures during pregnancy and lactation.

Trained study staff conducted up to four semi-structured telephone interviews with participants: at enrolment (before gestational week 20), ~24 and 32 weeks' gestation, and as soon as possible after delivery. Interviewers collected data from participants regarding race, ethnicity, socio-economic status (Hollingshead categories based on maternal and paternal education and occupation; possible range from highest = 1 to lowest = 5) [46], reproductive history, pre-pregnancy weight and height, comorbidities, smoking and alcohol use, pregnancy outcomes, and name, dose and dates of medication use [44]. Furthermore, interviewers administered self-assessment questionnaires to measure disease severity. These included the HAQ (a validated measure of functional status in patients with RA; possible range from 0 = no disability to 3 = completely disabled) [47, 48], 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). Medical records were requested from participants to help verify maternal report.

Pregnant women with a last menstrual period between 2003–2014 were eligible if they enrolled before gestational day 140 (Fig. 1) in either (i) MotherToBaby Autoimmune Diseases in Pregnancy Study and reported having RA or IBD (either Crohn's disease or ulcerative colitis) or (ii) MotherToBaby Asthma Medications in Pregnancy Study and reported having asthma ($n = 1112$). Women who were lost to follow-up, withdrew, had an incomplete postpartum interview or had a spontaneous or therapeutic abortion were excluded. Women meeting the basic inclusion criteria ($n = 960$) were included in RA, IBD or asthma subcohorts according to diagnoses. Women were excluded if missing a start or stop date for medications of interest (Fig. 1). For analyses considering OCS dose, we excluded women missing OCS dose information during the relevant exposure windows (Fig. 1; $n = 4$ for RA, $n = 1$ for IBD).

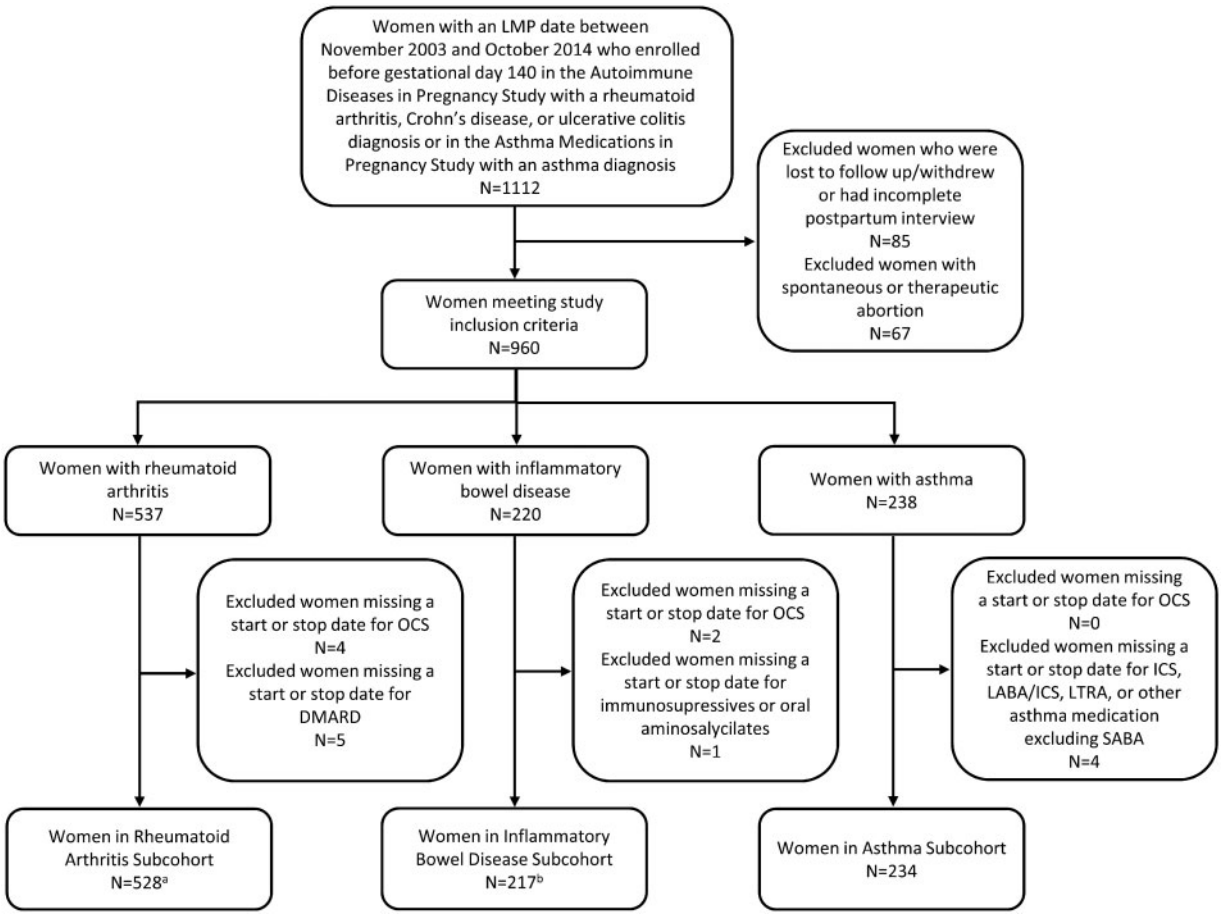
Outcome

Gestational age at delivery was calculated from the last menstrual period date with adjustment for discrepant ultrasound measurements. Still birth and live birth deliveries were classified as preterm (primary outcome) based on delivery between 20 (140 gestational days, i.e. after the timeframe for spontaneous abortion) and <37 gestational weeks (<259 gestational days) and as early PTB (exploratory outcome) based on delivery between 20 and <34 weeks.

Exposure modeling

OCS use was the main exposure of interest. OCS daily dose on each gestational day was calculated based on reported dates of use, dose and frequency of use, and doses were converted to prednisone equivalent dose [49]. OCS average daily dose was the mean daily dose across days with any OCS use. OCS cumulative dose on each day was calculated by summing daily dose on each previous day. Other RA-related medications of interest were biologic DMARD (B-DMARD) and non-biologic DMARD (NB-DMARD).k-means is a statistical method used to group individuals with similar patterns of a measurement [50]. To evaluate the impact of OCS dose earlier in pregnancy on PTB risk, we used k-means to cluster women with similar trajectories of OCS dose during the first 139 days of pregnancy with the R statistical software package 'kml' [32, 50, 51]. We selected this method because it makes no *a priori* assumptions about trajectory shape or membership [50], and it has been used previously to characterize patterns of medications in

Fig. 1 Study cohort diagram



Fifteen women were in both the rheumatoid arthritis and IBD subcohorts, 11 women were in both the RA and asthma subcohorts, seven women were in both the IBD and asthma subcohorts, and one woman was in all three subcohorts. LMP: last menstrual period; OCS: oral corticosteroid; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LTRA: leukotriene receptor agonist; SABA: short-acting beta-agonist. [a]$n = 524$ women with oral corticosteroid dose information available before gestational day 140, $n = 525$ women with oral corticosteroid dose information available after gestational day 109. [b]$n = 216$ women with oral corticosteroid dose information available before gestational day 140.

pregnancy [32, 52–54]. We considered daily and cumulative dose on each gestational day allowing up to $k = 3$ clusters; we selected three clusters based on sample size of the smallest cluster. We plotted the mean dose for each cluster (i.e. trajectory group) on each day as well as each woman's trajectory. Because of pronounced differences between individual trajectories and daily dose cluster means (Supplementary Fig. S1, available at *Rheumatology* online) due to sporadic OCS use, we focused the trajectory-PTB analysis on cumulative dose.

Because PTB can occur as early as gestational day 140, we could not apply the trajectory method when considering OCS dose later in pregnancy, as pregnancies would need the same gestational length to avoid including postpartum days for those with shorter gestations [32]. Furthermore, we avoided assessing cumulative dose or a fixed exposure window after gestational day 139 because pregnancies with shorter gestations would have less opportunity for exposure, which could cause immortal time bias [55]. Therefore, to evaluate the impact of OCS use later in pregnancy on PTB, we assessed time-dependent exposure on each gestational day between day 140 and 259, allowing for daily changes in use (any/none) and dose (high/low/none). In the primary analysis, an additional 30 days of exposure was included after OCS and DMARD end dates to allow for potential residual immunosuppressive or anti-inflammatory effects to impact intrauterine infection. Therefore, in addition to use after gestational day 139, we also considered use of these medications in the 30 days before gestational day 140 (i.e. starting on gestational day 110) to define exposure. Daily doses equivalent to $\geqslant 10$ mg of prednisone were considered to be high, as previous studies indicated increased infection risk around 10 mg of prednisone

[7–11]. In sensitivity analyses, we took two other approaches to time-dependent exposure modeling. First, exposed person-time ended on the reported end dates, i.e. the 30 additional days of exposure were removed. Second, in an intention-to treat analysis, exposed person-time began with the earliest reported start date of medication use after gestational day 139 and continued until censoring (described below) [55]. In sensitivity and dose analyses, we collapsed B-DMARD and NB-DMARD exposures into DMARD exposure given similar PTB rates.

Statistical analysis

We used modified Poisson regression to estimate risk ratios (RR) and 95% CI between trajectory group before gestational day 140 and PTB [56]. With time since gestational day 140 as the time scale, we used Cox proportional hazard models to estimate hazard ratios (HR) for medication exposure after gestational day 139 and PTB. Women were censored at gestational day 259 if their delivery date was after that (i.e. not preterm). Due to the limited number of PTBs, we used propensity scores, described below, to adjust for potential confounders [57]. First, we estimated crude associations using one model for each medication exposure. Then, we adjusted each model for the propensity score. Finally, we mutually adjusted for all medications and propensity scores within one model. Due to limited size, we reported early PTB risk by OCS exposure during the first half of pregnancy only.

Potential confounders considered for adjustment by propensity score included: last menstrual period year, gestational age at enrolment, maternal age, race and ethnicity, socio-economic status (Hollingshead categories [46]), primiparity, multiple gestation, $\geqslant 5$ servings of alcohol in the first trimester, cigarette smoking in the first trimester, pre-pregnancy overweight or obesity, history of diabetes, history of hypertension, autoimmune disease comorbidities, NSAID use during the first half of pregnancy, and disease severity measures at enrolment as continuous variables. For analyses of exposures after gestational day 139, we also considered for adjustment cumulative OCS dose trajectory (high/low/none) and use of other medications of interest (any/none) during pregnancy and before the start of the exposure window. We estimated propensity scores for each medication exposure group during each exposure window. For time-varying exposures, the propensity score was calculated based on any exposure to a medication of interest after gestational day 139, classifying those with both high and low dose exposures as having high dose. We included in the propensity score models variables that were associated with both the outcome and the exposures, with the exception of race/ethnicity and maternal age, which we included regardless of their association with exposure and outcome. We imputed missing values with single imputation for HAQ ($n = 3$), pain score ($n = 2$), and global patient score ($n = 2$), using predictors of the variables. To explore the impact of adjusting for factors related to disease severity, we removed self-assessed measures of disease severity at the time of enrolment and use of medications of interest before the start of the exposure window from the propensity score models predicting exposure after gestational day 139.

Results

The median gestational age at enrolment was 75 days for RA ($n = 528$), 70 days for IBD ($n = 217$), and 90 days for asthma ($n = 234$) subcohorts. Maternal characteristics are described by non-mutually exclusive medication exposure groups in the second half of pregnancy in Table 1 (RA) and Supplementary Tables S1–2, available at *Rheumatology* online (IBD and asthma). Women were primarily non-Hispanic White with the highest levels of socioeconomic status, and the average maternal age was at least 31 years across all medication groups. The highest RA severity and lowest asthma control were observed among women with OCS exposure. PTB risk was 15.5% ($n = 82$) for RA, 14.3% ($n = 31$) for IBD and 8.6% ($n = 20$) for asthma.

RA: OCS dose earlier in pregnancy and PTB

For clusters of OCS cumulative dose trajectories during the first 139 gestational days, the low trajectory had a mean cumulative dose of 264.9 mg (Table 2; Fig. 2), the medium trajectory had a mean cumulative dose of 883.0 mg, and the high trajectory, with only 15 women, had a mean cumulative dose of 2, 208.6 mg prednisone equivalent, with the highest total number of days of OCS use of 137 days and the highest average daily dose of 16.1 mg prednisone equivalent. Compared with no OCS use before gestational day 140, PTB risk was increased in the high (adjusted (a) RR: 4.77 (95% CI: 2.76, 8.26); Table 3) and medium (aRR: 1.81 (95% CI: 1.10, 2.97)) cumulative dose trajectory groups. The low cumulative dose trajectory group was associated with an increased PTB risk that was not statistically significant (aRR: 1.38 (95% CI: 0.79, 2.38)). DMARD use before gestational day 140 was not associated with PTB (b-DMARD aHR: 1.08 (95% CI: 0.70, 1.66); nb-DMARD aHR: 0.87 (95% CI: 0.55, 1.38)).

Risk of early PTB was 2.2% ($n = 6$) among women with no OCS use before day 140, and was 26.7% ($n = 4$), 3.3% ($n = 4$) and 3.4% ($n = 4$), respectively, in the high, medium and low trajectory groups.

RA: OCS exposure later in pregnancy and PTB

The aHR for OCS exposure after gestational day 139, as compared with no OCS exposure during that time was 1.64 (95% CI: 0.92, 2.92; Table 4). DMARDs were not associated with an increased PTB rate (B-DMARD aHR: 0.91 (95% CI: 0.56, 1.47); NB-DMARD aHR: 0.90 (95% CI: 0.48, 1.68)). Exposure to $\geqslant 10$ mg of prednisone equivalent dose after gestational day 139 was associated with an increased PTB rate (aHR: 2.45, 95% CI: 1.32, 4.56; Table 4), whereas <10 mg was associated with a modest increased PTB rate that was not statistically significant (aHR: 1.18 (95% CI: 0.60, 2.30)).

Table 1 Characteristics among women in the RA subcohort by exposures (not mutually exclusive), $n = 528$

Characteristic	Any exposure after gestational day 139[a]					
	Oral corticosteroid		B-DMARD		NB-DMARD	
	Yes *n*=250	No *n*=278	Yes *n*=208	No *n*=320	Yes *n*=96	No *n*=432
LMP Year 2009–2014, n (%)	121 (48.4)	155 (55.8)	118 (56.7)	158 (49.4)	65 (67.7)	211 (48.8)
Maternal age, mean (SD)	32.3 (4.6)	32.3 (4.7)	32.6 (4.5)	32.1 (4.7)	32.3 (4.6)	32.3 (4.6)
Non-Hispanic White, n (%)	196 (78.4)	221 (79.5)	174 (83.7)	243 (75.9)	76 (79.2)	341 (78.9)
Socioeconomic status, Hollingshead categories 1 or 2[b], *n* (%)	197 (78.8)	213 (76.6)	166 (79.8)	244 (76.3)	74 (77.1)	336 (77.8)
Primiparous, *n* (%)	120 (48.0)	129 (46.4)	99 (47.6)	150 (46.9)	42 (43.8)	207 (47.9)
Multiple gestation, *n* (%)	16 (6.4)	7 (2.5)	11 (5.3)	12 (3.8)	2 (2.1)	21 (4.9)
$\geqslant$5 servings of alcohol in the first trimester, *n* (%)	41 (16.4)	56 (20.1)	28 (13.5)	69 (21.6)	14 (14.6)	83 (19.2)
First trimester cigarette smoking, *n* (%)	14 (5.6)	19 (6.8)	9 (4.3)	24 (7.5)	4 (4.2)	29 (6.7)
Pre-pregnancy hypertension, *n* (%)	20 (8.0)	17 (6.1)	20 (9.6)	17 (5.3)	11 (11.5)	26 (6.0)
IBD, lupus, or ankylosing spondylitis, *n* (%)	16 (6.4)	13 (4.7)	15 (7.2)	14 (4.4)	3 (3.1)	26 (6.0)
NSAID use before gestational day 110, *n* (%)	102 (40.8)	86 (30.9)	76 (36.5)	112 (35.0)	41 (42.7)	147 (34.0)
Oral corticosteroid use before gestational day 110, *n* (%)	205 (82.0)	39 (14.0)	83 (39.9)	161 (50.3)	53 (55.2)	191 (44.2)
B-DMARD use before gestational day 110, *n* (%)	172 (68.8)	183 (65.8)	207 (99.5)	148 (46.3)	63 (65.6)	292 (67.6)
NB-DMARD use before gestational day 110, *n* (%)	88 (35.2)	71 (25.5)	58 (27.9)	101 (31.6)	88 (91.7)	71 (16.4)
HAQ at enrollment, mean (SD)[c]	0.67 (0.67)	0.40 (0.52)	0.49 (0.60)	0.56 (0.62)	0.47 (0.58)	0.54 (0.62)
Pain score at enrollment, mean (SD)[d]	34.4 (29.5)	23.7 (25.3)	27.2 (27.7)	29.7 (28.0)	24.8 (26.5)	29.6 (28.2)
Global score at enrollment, mean (SD)[d]	29.9 (27.1)	19.9 (23.1)	22.7 (24.5)	26.0 (26.2)	20.5 (22.9)	25.6 (26.0)

[a]An additional 30 days of exposure was added to reported end dates of use. [b]Calculated using Hollingshead categories based on maternal and paternal education and occupation; Possible Range: 1, highest to 5, lowest. Missing for eight women. [c]Imputed for three women; possible range: 0, no disability to 3, completely disabled. [d]Imputed for two women; pain score possible range: 0, no pain to 100, severe pain; patient's global score possible range: 0, very well to 100, very poor. B-DMARD: biologic disease modifying antirheumatic drug; LMP: last menstrual period; NB-DMARD: non-biologic disease modifying antirheumatic drug.

Table 2 OCS exposure between LMP and day 139 by trajectory group for RA ($n = 254$)

Trajectory group	*n*	Total number of days of oral corticosteroid use		Average daily prednisone equivalent dose[a] (mg)		Total cumulative prednisone equivalent dose (mg)	
		Min, Max	Mean (S.D.)	Min, Max	Mean (S.D.)	Min, Max	Mean (S.D.)
High dose trajectory	15	134, 139	137 (1.5)	11.5, 25.0	16.1 (3.2)	1580, 3350	2208.6 (432.1)
Medium dose trajectory	122	13, 139	123.7 (26.7)	4.6, 55.4	8.0 (5.8)	410, 2010	883.0 (273.5)
Low dose trajectory	117	1, 139	45.4 (36.5)	1.0, 41.7	7.0 (5.2)	10, 960	264.9 (206.4)

[a]Average dose on days with oral corticosteroid use. max: maximum; min: minimum.

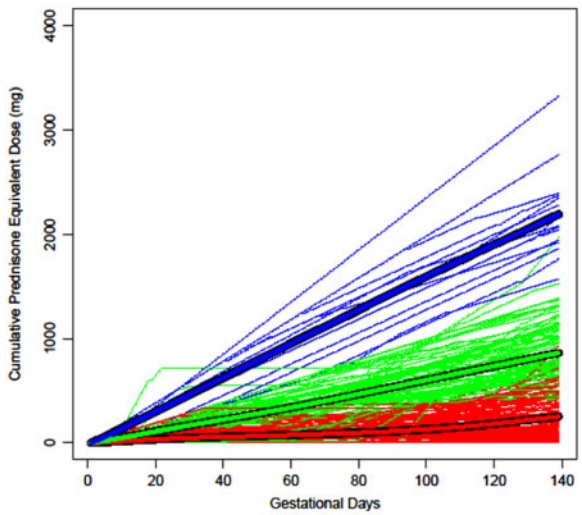
Point estimates for OCS exposure tended to attenuate with adjustment for potential confounders and then strengthen slightly when including all medication exposures in the same model. Compared with including factors related to disease severity, adjusted associations for OCS exposure and PTB tended to be less attenuated when they were omitted (Supplementary Table S3, available at *Rheumatology* online). In sensitivity analyses, results tended to be strengthened when removing the 30 additional days of exposure following end dates or when classifying as exposed all person-time following the earliest medication use after gestational day 139 (Supplementary Table S4, available at *Rheumatology* online).

Exploratory analysis for IBD and asthma

For IBD, estimates of the association between cumulative dose trajectory group during the first 139 days (Supplementary Table S5 and Supplementary Fig. S2,

available at *Rheumatology* online) and PTB were imprecise and were unadjusted (Supplementary Table S6, available at *Rheumatology* online; high group HR: 2.17 (95% CI: 0.63, 7.45); low group HR 1.34 (95% CI: 0.59, 3.05)). For asthma, any OCS exposure during the first half of pregnancy was associated with a suggested increased PTB risk (Supplementary Table S6, available at *Rheumatology* online; aRR 2.15 (95% CI: 0.83, 5.60)). Estimates were imprecise (Supplementary Table S7, available at *Rheumatology* online); however, exposure to OCSs overall after day 139 was not strongly associated with PTB in the IBD (Supplementary Table S7, available at *Rheumatology* online; aHR 1.09 (95% CI: 0.45, 2.60)) and asthma (aHR 1.22 (95% CI: 0.27, 5.50)) subcohorts. For IBD, unadjusted HRs for exposure to ⩾20 mg of prednisone equivalent dose after day 139 were 2.06 (95% CI: 0.84, 5.04) and 0.68 (95% CI: 0.09, 5.04)) for <20 mg (Supplementary Table S8, available at *Rheumatology* online). Other medications of interest for IBD and asthma were not strongly associated with an increased PTB risk (Supplementary Tables S6–8, available at *Rheumatology* online).

Fig. 2 Oral corticosteroid cumulative dose trajectories between the last menstrual period and gestational day 139 ($n = 254$)



The thick lines represent the mean cumulative dose on each gestational day for each group and the thin lines represent each woman's observed trajectory; blue = high, green = medium and red = low dose trajectories.

Comment

Among women with RA, there was a suggestion of trend for increasing cumulative OCS dose during the first half of pregnancy and increased PTB risk. High and medium dose trajectories were associated with an increased PTB risk compared with no OCS exposure. However, the lowest trajectory was associated with a more modest increased PTB risk that was not statistically significant. Doses of OCS ⩾10 mg of prednisone equivalent later in pregnancy were associated with an ~2.5-fold increased PTB rate. However, PTB rate was not significantly increased for doses <10 mg. B-DMARD and NB-DMARD exposure earlier and later in pregnancy were not associated with PTB.

Exploratory analysis for early PTB suggested an increased risk among those with the highest OCS doses; however, the association should be confirmed in a study with adequate power for PTB subtypes. In exploratory analyses for IBD and asthma, estimates were

Table 3 Association between exposures before day 140 and preterm birth for RA ($n = 524$)

Medication exposure before gestational Day 140[a]	n	Preterm birth	% Preterm birth	Crude RR (95% CI)	Adjusted RR[b] (95% CI)	Mutually adjusted RR[c] (95% CI)
Oral corticosteroid						
High dose trajectory	15	10	66.7	6.92 (4.15, 11.55)	4.77 (2.76, 8.26)	4.74 (2.72, 8.25)
Medium dose trajectory	122	28	23.0	2.38 (1.46, 3.89)	1.81 (1.10, 2.97)	1.87 (1.13, 3.10)
Low dose trajectory	117	17	14.5	1.51 (0.85, 2.67)	1.38 (0.79, 2.38)	1.38 (0.80, 2.40)
No oral corticosteroid	270	26	9.6	Reference	Reference	Reference
B-DMARD	354	55	15.5	1.02 (0.66, 1.56)	1.08 (0.70, 1.66)	1.07 (0.71, 1.61)
No B-DMARD	170	26	15.3	Reference	Reference	Reference
NB-DMARD	161	23	14.3	0.89 (0.57, 1.40)	0.87 (0.55, 1.38)	0.85 (0.55, 1.30)
No NB-DMARD	363	58	16.0	Reference	Reference	Reference
No medication of interest	56	4	7.1	NA	NA	NA

[a]Mutually exclusive oral corticosteroid trajectory groups and any *vs* none B-DMARD and NB-DMARD exposure groups. [b]One model for each medication of interest. RR adjusted for quintiles of the propensity score: last menstrual period year (<2009, ⩽2009), maternal age, race and ethnicity (Non-Hispanic White, Other), multiple gestation, ⩾5 servings of alcohol in the first trimester, autoimmune disease comorbidity (IBD, lupus or ankylosing spondylitis), non-steroidal anti-inflammatory drug use before gestational day 140 (any, none), and HAQ Disability Index, pain score and global score at enrolment. [c]One model, adjusting for each medication exposure group of interest and each associated propensity score. B-DMARD, biologic disease modifying antirheumatic drug; NB-DMARD, non-biologic disease-modifying antirheumatic drug; RR, risk ratio.

TABLE 4 Association between exposures after day 139 and preterm birth for RA

Time-dependent medication exposure after gestational day 139[a]	*n*	Preterm birth	Person-weeks	Rate (per 1000/week)	Crude HR (95% CI)	Adjusted HR[b] (95% CI)	Mutually adjusted HR[c] (95% CI)
Oral corticosteroid	253	51	4530	11.3	2.81 (1.80, 4.39)	1.64 (0.92, 2.92)	1.83 (1.01, 3.32)
No oral corticosteroid	368	31	7415	4.2	Reference	Reference	Reference
B-DMARD	215	25	4146	6.0	0.90 (0.56, 1.44)	0.91 (0.56, 1.47)	0.85 (0.52, 1.37)
No B-DMARD	389	57	7798	7.3	Reference	Reference	Reference
NB-DMARD	102	12	2092	5.7	0.83 (0.45, 1.53)	0.90 (0.48, 1.68)	0.94 (0.49, 1.78)
No NB-DMARD	447	70	9852	7.1	Reference	Reference	Reference
No medication of interest	234	18	4044	4.5	NA	NA	NA
Oral corticosteroid $\geqslant$10 mg/day[d]	141	32	1836	17.4	4.57 (2.79, 7.49)	2.45 (1.32, 4.56)	2.47 (1.32, 4.63)
Oral corticosteroid $<$10 mg/day[d]	177	19	2610	7.3	1.80 (1.02, 3.19)	1.18 (0.60, 2.30)	1.23 (0.63, 2.41)
No oral corticosteroid	371	31	7469	4.2	Reference	Reference	Reference
DMARD	266	33	5263	6.3	0.90 (0.58, 1.39)	0.89 (0.57, 1.41)	0.88 (0.56, 1.40)
No DMARD	335	49	6606	7.4	Reference	Reference	Reference
No medication of interest	232	18	4074	4.4	NA	NA	NA

[a]An additional 30 days of exposure was added to reported end dates of use for oral corticosteroids and DMARDs. [b]One model for each medication of interest. HR adjusted for quintiles of the propensity score: last menstrual period year ($<$2009, $\leqslant$2009), maternal age, race and ethnicity (Non-Hispanic White, Other), multiple gestation, $\geqslant$5 servings of alcohol in the first trimester, autoimmune disease comorbidity (IBD, lupus or ankylosing spondylitis), oral corticosteroid cumulative dose trajectory before gestational day 110 (high, low, none), non-steroidal anti-inflammatory drug before gestational day 110 (any, none) and HAQ Disability Index, pain score and global score at enrolment. [c]One model, adjusting for each medication exposure group of interest and each associated propensity score. [d]Prednisone equivalent dose. B-DMARD, biologic disease modifying antirheumatic drug; HR, hazard ratio; NA, not applicable; NB-DMARD, non-biologic disease-modifying antirheumatic drug.

imprecise. Nevertheless, for asthma, there was a suggested increase in PTB following OCS use, especially during the first half of pregnancy. For IBD, there was a suggested increase in PTB for high OCS dose, although estimates were imprecise and were unadjusted for confounders. Overall, IBD and asthma exploratory analyses align with the direction of the associations in the RA analysis despite limitations of precision and inability to adjust for IBD severity.

Building upon our previous report that patterns of higher *vs* lower prednisone dose during the first 32 gestational weeks were associated with shorter gestation among women with RA [32], we found that higher OCS doses in two time windows (i.e. earlier and later in pregnancy) *vs* no OCS use were positively associated with the clinically-relevant outcome of PTB. Although unadjusted for confounders, other studies reported that prednisone dose $>$10 mg/day anytime during pregnancy was associated with PTB in women with systemic lupus erythematosus [25], whereas gestational age at delivery did not differ significantly between prednisone dose $>$7.5 mg/day *vs* $\leqslant$7.5 mg/day anytime during pregnancy in women with RA [23].

OCS dose during pregnancy is tightly linked with disease activity [3], and maternal autoimmune disease and disease control/activity are also associated with increased PTB risk [29, 33–43]. Therefore, confounding by disease severity would be expected to bias the OCS dose–PTB association upward. We adjusted for self-assessed RA severity at enrolment, usually during the first trimester, and for disease-related medication exposures earlier in pregnancy when considering exposures later in pregnancy. Adjusting for factors related to disease severity tended to attenuate point estimates. Ideally, we would have measures of disease severity at the time of every medication start, stop or dose change to account for time-varying confounding later in pregnancy [58].

In accordance with our hypothesis, high OCS doses later in pregnancy were associated with an increase in PTB. This positive association could be due to a true effect of OCS on PTB, for example by OCS contributing to subclinical intrauterine infection and triggering PTB as previously proposed [13], in combination with residual confounding by time-varying severity. However, the link between OCS dose and PTB was also observed for OCS exposures earlier in pregnancy. This could be due to a direct effect of OCS dose early in pregnancy on PTB development, an indirect effect of OCS dose early in pregnancy on PTB through OCS dose later in pregnancy, and/or time-varying confounding by disease severity. Lending support to the hypothesis that OCS-related infection contributes to PTB, Desai *et al.* reported that increasing steroid dose was associated with an increased serious infection risk among pregnant women with autoimmune conditions [7]. This association was independent of NB-DMARDs and tumor necrosis factor inhibitors, which were not associated with infection, just as they were not associated with PTB in our study.

Associations were strongest when removing the additional 30 days of exposure in sensitivity analyses indicating that future studies of OCS and PTB should not take this approach. Our study had limitations in addition to being unable to account for time-varying confounding of OCS dose and PTB by disease severity changes. First, we did not systematically collect clinical information to characterize type of RA, such as presence of erosions and rheumatoid factor and anti-citrullinated protein antibody positivity. Second, the limited study size led to imprecise results, especially in our exploratory analyses for IBD and asthma. It also prevented us from thorough examination of PTB subtypes (early/late, spontaneous/indicated) [59], which have been differentially associated with subclinical chorioamnionitis [60], and the interaction between OCS and B-DMARDs, as infection risk may be greatest among individuals using both treatments [61]. Third, women may have under-reported doses or medication use duration, possibly resulting in upward bias for the associations between low OCS dose and PTB. Nevertheless, maternal self-report of OCS use among women with RA and asthma appears to be more complete than information from medical records alone [44]. Fourth, results may reflect selection bias if loss to follow-up and pregnancy loss are associated with the exposures and PTB. Fifth, women with RA tended to have relatively low disease severity, and the observed associations may not generalize to women with greater disease activity. Women were primarily non-Hispanic white with older maternal age and higher socio-economic status, although these factors are not expected to modify the associations. Finally, we were unable to evaluate the hypothesized mechanism between OCS and PTB through subclinical intrauterine infection because placental pathology was unavailable. Combining all OCS doses together into one exposure may result in a positive or null association between OCS and PTB depending on the distribution of OCS doses used in a study population, and evaluating OCS dose instead of any OCS use provides nuanced information about associations with perinatal outcomes. The positive association between high dose OCS and PTB observed among women with RA in this study may reflect residual confounding by underlying disease severity or an effect of OCS at high doses or a combination of confounding and medication effect. However, the lack of a clear positive association between low OCS dose, b-DMARDs, and nb-DMARDs and PTB is reassuring for women who are able to manage RA with low OCS doses and DMARDs during pregnancy.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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