Journal of Psychiatric Research 104 (2018) 100–107

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Predictors of severe relapse in pregnant women with psychotic or bipolar disorders

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ARTICLE INFO

Keywords:
Psychosis
Bipolar
Pregnancy
Relapse
Medication

ABSTRACT

Pregnancy in women with severe mental illness is associated with adverse outcomes for mother and infant. There are limited data on prevalence and predictors of relapse in pregnancy. A historical cohort study using anonymised comprehensive electronic health records from secondary mental health care linked with national maternity data was carried out. Women with a history of serious mental illness who were pregnant (2007–2011), and in remission at the start of pregnancy, were studied; severe relapse was defined as admission to acute care or self-harm. Predictors of relapse were analysed using random effects logistic regression to account for repeated measures in women with more than one pregnancy in the study period. In 454 pregnancies (389 women) there were 58 (24%) relapses in women with non-affective psychoses and 25 (12%) in women with affective psychotic or bipolar disorders. Independent predictors of relapse included non-affective psychosis (adjusted OR = 2.03; 95% CI = 1.16–3.54), number of recent admissions (1.37; 1.03–1.84), recent self-harm (2.24; 1.15–4.34), substance use (2.15; 1.13–4.08), smoking (2.52; 1.26–5.02) and non-white ethnicity (black ethnicity: 2.37; 1.23-4.57, mixed/other ethnicity: 2.94; 1.32-6.56). Women on no regular medication throughout first trimester were also at greater risk of relapse in pregnancy (1.99; 1.05–3.75). There was no interaction between severity of illness and medication status as relapse predictors. Therefore, women with non-affective psychosis and higher number of recent acute admissions are at significant risk of severe relapse in pregnancy. Continuation of medication in women with severe mental illness who become pregnant may be protective.

1. Introduction

Relapse of serious mental illness (SMI; schizophrenia, related delusional disorders, affective psychoses and bipolar disorder) in the perinatal period is potentially devastating for a woman and her unborn baby. It may impact on her ability to care for herself, and rarely but tragically result in custody loss of children, suicide or infanticide (Jones et al., 2014). International confidential enquiries into maternal deaths highlight psychiatric illness as a leading cause (Austin et al., 2007; Cantwell et al., 2011; Khalifeh et al., 2016).

Studies have consistently reported increased risk of relapse of psychosis in the early postpartum, with risk factors including history of bipolar disorder or post-partum psychosis (Jones et al., 2014; Munk-Olsen et al., 2009; Wesseloo et al., 2015). There are fewer data on the course of SMI during pregnancy, particularly for schizophrenia. Recently reported data indicated a 12% rate of hospitalisation for women with schizophrenia in pregnancy (Rochon-Terry et al., 2016). For bipolar disorder some studies estimate around 8–18% relapse in pregnancy (Di Florio et al., 2013; Grof et al., 2000), but tertiary perinatal mental health clinics have reported substantially higher rates (71%), particularly in women who discontinue medication (86%) and those with more severe illness (Viguera et al., 2007). Varying definitions of relapse may explain inconsistencies; some use hospital admission and others use clinical or research interviews to determine symptomatology, which identify less severe relapses.

We aimed to investigate risk and predictors of severe relapse in

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https://doi.org/10.1016/j.jpsychires.2018.06.019
Received 8 February 2018; Received in revised form 18 June 2018; Accepted 29 June 2018

pregnancy in a cohort of women with SMI. We hypothesised that: 1) diagnosis and markers of severity (non-affective SMI, recent admissions) and 2) first trimester medication changes (switching or discontinuation) would be independently associated with relapse. We also explored interactions between diagnosis, admissions in two years before pregnancy and domestic violence (DV) with medication.

2. Methods

2.1. Data source

Data came from the South London and Maudsley (SLaM) NIHR Biomedical Research Centre Clinical Record Interactive Search (CRIS) (Stewart et al., 2009), a large resource of comprehensive secondary mental health records from over 300,000 patients. SLaM serves a catchment of around 1.2 million residents from four London boroughs, and provides some tertiary services. CRIS allows searching and retrieval of anonymised clinical records within robust technical and procedural safeguards (Fernandes et al., 2013). Data can be extracted from free text (e.g. case notes and correspondence), using targeted keyword searches. Structured data include socio-demographics (including ethnicity), year and month of birth, and referrals data including admissions to SLAM and movements within SLaM services such as wards and community teams. Several natural language processing (NLP) applications on a General Architecture for Text Engineering (GATE) platform (Cunningham et al., 2013) have been developed which derive structured data from free text and are validated against manual annotations. These include diagnosis and medication (Perera et al., 2016). CRIS was approved for research by Oxfordshire Research Ethics Committee C (08/H0606/71 + 5), and is linked to Hospital Episode Statistics: national data for inpatient, outpatient and accident and emergency attendances in England including maternity data (NHS Digital, formerly The Health Social Care Information Centre).

2.2. Study population

A historic cohort was assembled of women pregnant from 2007 to 2011 whose pregnancies continued beyond first trimester. We used maternity Hospital Episode Statistics (HES) indicating delivery of a baby linked to CRIS data indicating women with SMI, using ICD-10 diagnoses F20, F22, F23, F25, F28, F29 (schizophrenia and related disorders, schizoaffective disorders and delusional disorders), F30, F31 (mania and bipolar disorders), F32.3, F33.3 (psychotic depression), F53.1 (puerperal psychosis). CRIS data is complete from 2006 and at the time of data extraction, HES data was available up to the end of 2011. HES data indicated the end date of pregnancy. In order to collect time dependent variables, trimesters of pregnancy were dated using a modified validated algorithm (Li et al., 2013; Taylor et al., 2015). CRIS data captured socio-demographic and clinical details regarding women's mental health. In order to be able to capture clinical details regarding women's mental health in the perinatal period, we included women under SLaM care (therefore on CRIS) at any point from 6 months before to 6 weeks after the HES delivery episode with SMI diagnoses during the preconception period so. We excluded women whose illness was not in remission at the start of pregnancy, determined by admission to acute mental health care (inpatient or home treatment) in the three months before the start date of pregnancy.

2.3. Measures

2.3.1. Severe relapse

The first severe relapse of SMI (hereafter termed relapse) occurring during pregnancy was measured. This has previously been defined as hospitalisation (Wesseloo et al., 2015). We defined it as admission to mental health inpatient care, referral for home treatment (services for acute mental health crisis in the UK, involving frequent home visits (Johnson et al., 2008)) or an episode of self-harm (see (Taylor et al., 2016)) so that all significant relapses were included. Admissions/referrals were extracted from structured CRIS data or HES inpatient admissions to mental health trusts outside SLaM. Self-harm during pregnancy was extracted using free text search terms previously validated in CRIS (Polling et al., 2015; Taylor et al., 2016).

2.3.2. Socio-demographic characteristics for index (first) pregnancy

Recorded ethnicity was categorised into 'Black African/Caribbean/other', 'White British/other', and 'Mixed, Asian or other/not stated'. Neighbourhood-level deprivation score was extracted closest in date to the beginning of pregnancy. These give a summary measure of socio-economic status at the level of the lower super output area (LSOA): a geographic unit containing a minimum of 1000 residents and 400 households with an average nationally of around 1500 residents (Noble et al., 2007). Manual searches of CRIS free text using piloted terms established number of children prior to pregnancy, relationship status in pregnancy, history of childhood abuse and DV before/during pregnancy and family history of mental illness. Recorded smoking in pregnancy was extracted by manual free text searches using terms (Wu et al., 2013).

2.3.3. Mental disorder characteristics and severity at the beginning of pregnancy

Diagnosis recorded at the start of pregnancy, extracted from CRIS structured fields and free text using an NLP application validated for dementia (Perera et al., 2016), was categorised into non-affective and affective. Non-affective SMI comprised schizophrenia, related psychoses, delusional disorders and schizoaffective disorders. Affective SMI comprised bipolar disorder, psychotic depression and history of postpartum psychosis. Where diagnosis was unclear, correspondence was scrutinised by a researcher and clinician.

Number of days in acute mental health care in the two years before pregnancy was extracted from CRIS (supplemented with HES for outside-SLaM care (Taylor et al., 2015)) and spells of acute care defined as periods of treatment in acute care (inpatient or home treatment) with at most 7 days between discharge and readmission. Time since last major episode was calculated from the beginning of the most recent 'spell' of acute care in the 2 years prior to conception. Detention under the Mental Health Act (involuntary admission) in the 2 years before pregnancy was extracted from structured fields and free text.

Manual free text searches of CRIS ascertained recorded alcohol and drug use in pregnancy within the previous 2 years, supplemented by substance misuse diagnoses from CRIS structured fields and an NLP application. Baseline level of functioning was estimated from the highest total adjusted score recorded in the two years before pregnancy from the Health of the Nation Outcome Scale (HoNOS), a routinely collected 12-item measure in UK mental health services of health and social functioning of people with severe mental illness (Wing et al., 1998) stored in CRIS.

2.3.4. Medication exposure in the first trimester of pregnancy

Medication exposures were extracted from free text in CRIS, primarily using an NLP application (validated for a number of antipsychotic agents (Kadra et al., 2015)) to extract structured indicators describing medication during the first trimester, supplemented by manual text searches. The clinical documents were recalled and manually coded for information on medications not already validated. Stops, starts and switches in regular antipsychotics, mood stabilisers and antidepressants were noted, including whether stops occurred abruptly (over 1–14 days) or gradually (> 14 days). Where speed of discontinuation was not specified, women were coded as stopping abruptly. Recorded non-adherence to medication was categorised if there was written concern about this. Two researchers rated medication, with consensus meetings to resolve uncertainties; a consecutive (26 pregnancies) were rated for identification of antipsychotic, mood

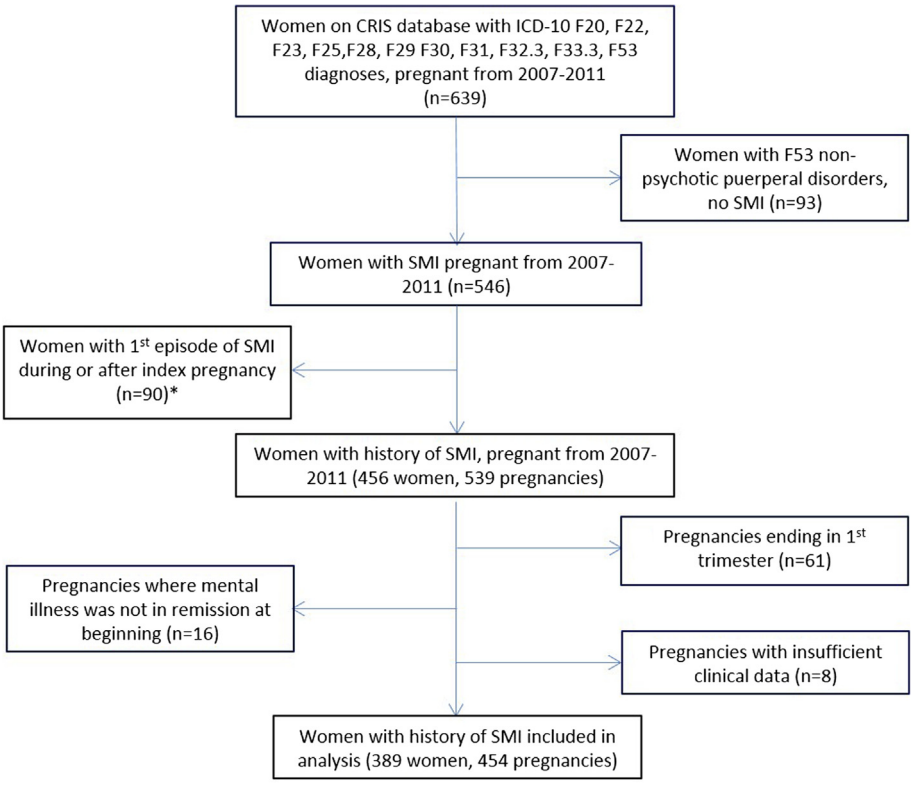

Fig. 1. Identification of women with SMI and pregnancies beyond first trimester.

stabiliser and antidepressant with inter-rater agreements of 97%. For the main analysis, medication was categorised as 'stopped or switched' if a woman had a stop and/or switch in a regular medication, 'continued' if a woman continued a regular medication all the way through the first trimester and did not stop or switch a regular medication, and 'no medication at start of pregnancy' if a woman was not on any regular medication at the start of 1st trimester. Further detail including exposures to individual medications and medication types in 3 months before pregnancy and 1st trimester is provided elsewhere (Taylor et al., 2015).

2.4. Data analysis

Data were analysed using STATA 12. After initial descriptive analyses of women, subsequent analyses were carried out by pregnancy. Incidence and timing (by trimester) of relapses during pregnancy were reported for the whole sample and stratified by baseline diagnosis. To account for non-independent data in women who contributed more than one pregnancy during the study period, all subsequent statistical analyses were carried out using random effects logistic regression. Only one indicator of acute mental health care before pregnancy – number of admissions – was used in multivariable analyses following chi^2 tests for association between them to assess colinearity. We used purposeful selection of variables (Bursac et al., 2008), and predictors with $p \leq 0.2$ from unadjusted analyses were added simultaneously to the model and unadjusted and fully adjusted effect sizes compared. Predictors with a fully adjusted p-value of > 0.5 were removed from the final model. Given our main hypothesis around medication; we ran post-hoc analyses using chi^2 tests to assess association of covariates with the medication variable using the 3 category medication variable as an outcome and random effects logistic regression to look at the association of medication with relapse, adjusted for each covariate separately to investigate confounding of the association with medication and relapse. Following a post-hoc test for colinearity between smoking and harmful substance use we ran the multivariable model excluding harmful substance use. Since women on no medication may be non-adherent or psychiatrically stable, we ran a test for the interaction of psychiatric stability (admission in the 2 years before pregnancy) and medication on relapse. Most research has investigated bipolar disorder so we also tested the interaction of medication with diagnosis on relapse and ran the analysis stratified by diagnostic group (affective/non-affective), reclassifying medication into two categories – continued versus stopped/switched/no medication. All interaction tests used the likelihood ratio.

A number of sensitivity analyses were carried out. To address issues of reverse causality for medication change and relapse both occurring in the first trimester, pregnancies with first trimester relapses were excluded, followed by an evaluation, censoring pregnancies which ended in the 2nd trimester. For comparability with other investigations of admissions in pregnancy, a sensitivity analysis excluded self-harm from the definition of relapse. To compare with previous studies on stopping medication and stopping abruptly in pregnancy (Viguera et al., 2007), women who switched a medication only were excluded from the 'stopped or switched' group (statistical power was insufficient to analyse switching separately) and we further excluded those stopping medication gradually. A further analysis excluded women with possible non-adherence in case of misclassification and we also reclassified women who continued a medication but were coded non-adherent into the stopped/switched group. Finally we looked at the unadjusted and adjusted associations with stopping versus switching/continuing an antidepressant, mood stabiliser and antipsychotic separately.

3. Results

3.1. Sample characteristics

There were 454 pregnancies in 389 women with history of SMI (Fig. 1). Fifty-two (13.4%) women had more than one pregnancy in the study period (number of pregnancies per woman ranged from 1 to 5).

Table 1
Socio-demographic and clinical characteristics of 389 pregnant women with severe mental illness.

	N = 389
Diagnosis at beginning of pregnancy, N (%)	
Affective	186 (47.8)
Non affective	203 (52.2)
Ethnicity, N(%)	
White British & other White	132 (33.9)
Black African & other Black	188 (48.3)
Asian/Mixed/Other	69 (17.7)
Deprivation score, median(range)[1]	34.9 (4.8,61.5)
Maternal age at 1st index delivery, mean(SD),	31.8 (6.1)
Partner during 1st index pregnancy	269 (69.2)
Number of children at 1st index pregnancy, N(%)	
0	182 (46.8)
1	103 (26.5)
≥2	104 (26.7)
Recorded history of child abuse, N(%)	78 (20.1)
Recorded domestic abuse before/during pregnancy, N(%)	133 (34.2)
Smoking in pregnancy, N(%)	69 (17.7)
Harmful substance use, N(%)	96 (24.7)
Self-harm in 2 years before pregnancy, N(%)	54 (13.9)
Number of days of acute care in 2 years before pregnancy, N(%)	
0	235 (60.4)
1-30	53 (13.6)
31-60	43 (11.1)
61+ (−537)	58 (14.9)
Number of acute admissions in 2 years before pregnancy, N(%)	
0	235 (60.4)
1	103 (26.5)
2	30 (7.7)
> 2	21 (5.4)
Time since last acute admission, N(%)	
None in 2 years before pregnancy	235 (60.4)
1 year	79 (20.3)
2 years	75 (19.3)
MHA[3] **in 2 years before pregnancy, N(%)**	67 (17.2)
Highest HoNOS total adjusted score in 2 years before pregnancy, median (range)[2]	12 (0–36)
Family history of any mental illness, N(%)	168 (43.2)
Medication changes 1st trimester, N(%)	
Continued	145 (37.3)
Stopped and/or switched	105 (27.0)
No medication at start	139 (35.7)

1: n = 374, 2: n = 196, 3: detained under section 2 or 3 of the mental health act.

Table 1 displays demographic and clinical characteristics of women. Of 203 (52.2%) women with diagnoses of non-affective SMI, 112 (28.8%) had diagnoses of schizophrenia or delusional disorder, 27 (6.9%) with schizoaffective disorder and 64 (16.5%) had other non-affective diagnoses including acute and transient psychosis; 186 (47.8%) women had affective diagnoses including bipolar disorder (138 women, 35.5%), depressive psychosis (41 women, 10.5%) and history of postpartum psychosis (7 women, 1.8%). Comorbid diagnoses between 9 months and 2 years before delivery episode included 18 (4.6%) women with substance use diagnoses, 9 (2.3%) with personality disorder diagnoses, 11 (2.8%) with anxiety disorders, 6 (1.5%) with learning difficulties and < 5 with other diagnoses including eating disorders, conduct disorders and epilepsy.

In 454 pregnancies, there were 83 (18.3%) relapses, including 74 (16.3%) admissions to acute care (inpatient or home treatment), with 26 (5.7%) relapses occurring in the first trimester and 32 (7.5%) in the second. Thirteen pregnancies ended in the second trimester, and of 383 remaining pregnancies a further 25 (6.5%) relapsed in third trimester. All admissions to the mother and baby unit were for acute mental health reasons. Supplementary Table 1 provides further detail on relapses by trimester and diagnosis.

First trimester medication (antidepressant, mood stabiliser or antipsychotic) exposures were as follows: 147 (15.7%) no regular medication, 240 (52.9%) receiving an antipsychotic, 67 (14.8%) a mood stabiliser and 106 (23.4%) an antidepressant; 188 (41.4%) exposed to one agent only, 88 (19.3%) exposed to two and 31 (6.8%) to more than two. Table 1 shows medication categories in the 1st trimester as used for analysis. Medication categories were associated strongly from one trimester to the next; from 3 months before pregnancy to 1st trimester, $chi^2 = 312.64$, $p < 0.001$, from 1st to 2nd trimester, $chi^2 = 296.41$, $p < 0.001$ and from 1st to 3rd trimester, $chi^2 = 182.34$, $p < 0.001$.

Deprivation scores were missing for 18 (4.0%) pregnancies. HoNOS scores were missing for 212 (46.7%).

3.2. Socio-demographic and clinical characteristics associated with relapse in pregnancy (Table 2) and associated with medication exposures (supplementary table 2)

Relapse in pregnancy was significantly associated with non-white ethnicity, DV, smoking, non-affective psychosis, substance misuse, admissions in the two years before pregnancy, less than 2 years since previous acute admission, and self-harm in the 2 years before pregnancy. Very similar results were found when relapses in the 1st trimester were excluded. Women who continued to take medication had fewer relapses than women who were medication free or stopped/switched medication but this was not statistically significant. Age, history of admissions variables, self-harm and smoking in pregnancy were distributed differently across medication groups. Average age was highest in the continued medication group. Women with pregnancies unexposed to medication tended to have less admissions or time in acute care in the two years before pregnancy. Rates of self-harm were highest in those who stopped or switched a medication and lowest in those who continued. Recorded smoking was highest in those who stopped or switched medication and lowest in those unexposed to medication at the beginning of pregnancy.

3.2.1. Multivariable analysis

In the fully adjusted model (Table 3), (adjusted for medication group, admissions and self-harm in 2 years before pregnancy, diagnosis at baseline, harmful substance use, smoking in pregnancy and ethnicity) relapse was independently associated with non-affective psychosis, illness severity (admissions and self-harm in two years before pregnancy), substance misuse, smoking in pregnancy and non-white ethnicity. Given substance misuse and smoking were strongly associated ($p < 0.001$), we also ran the model excluding substance misuse, which made no difference to our findings. Women not on medication were more likely to relapse than women who continued medication; stopping or switching medication was not associated with increased risk of relapse (Tables 3 and 4). However, when first trimester relapses were excluded, the association between being on no medication and relapse was attenuated (adjusted OR = 1.43; 95%CI 0.69–2.98). Post-hoc analysis showed the association with relapse was most confounded by admissions in 2 years before pregnancy and smoking (Supplementary Table 3). Stratified by affective/non-affective diagnosis (Supplementary Table 4), findings were similar, though due to smaller numbers most associations did not reach statistical significance. No significant interactions were found on risk of relapse between medication and affective/non-affective diagnosis ($chi2 = 0.01$, $p = 0.922$) and medication and admissions in the 2 years before pregnancy ($chi2 = 0.52$, $p = 0.471$), or between DV and medication status ($chi2 = 1.34$, $p = 0.248$).

3.3. Sensitivity analyses

Defining relapse by acute admissions only (n = 74 relapses) made little difference to results. Excluding pregnancies where medication was stopped gradually (n = 13) made no meaningful difference (Table 4). Excluding those with recorded non-adherence to address potential misclassification of medication (17 pregnancies) strengthened the

Table 2
Socio-demographic and clinical characteristic, and associations with relapse in pregnancy episodes (n = 454).

	N	N (%) relapse in pregnancy (n = 83)	Odds ratio (95% CI)	p-value
Baseline Diagnosis				
Affective	216	25 (11.6)	**Ref**	
Non affective	238	58 (24.4)	2.58 (1.45,4.58)	0.001*
Ethnicity				
White British & other White	221	49 (22.2)	**Ref**	
Black African & other Black	154	17 (11.0)	2.50 (1.24,5.04)	0.010*
Asian/Mixed/Other	79	17 (21.5)	2.31 (1.01,5.25)	0.047*
Partner during pregnancy[b]	321	58 (18.1)	0.94 (0.53,1.65)	0.826
Children at index pregnancy				
0	188	35 (18.6)	Ref	
1	127	25 (19.7)	1.06 (0.58,1.98)	0.836
≥2	139	23 (16.6)	0.83 (0.44,1.57)	0.563
Victim of child abuse[b]	96	22 (22.9)	1.44 (0.80,2.60)	0.221
Victim of domestic abuse before or during pregnancy[b]	167	39 (23.4)	1.74 (1.02,2.98)	0.044*
Smoking in pregnancy[b]	79	31 (39.2)	4.47 (2.23,8.99)	< 0.001*
Harmful substance use[b]	109	36 (33.0)	3.37 (1.82,6.21)	< 0.001*
Self-harm in 2 years before pregnancy[b]	61	23 (37.7)	3.60 (1.83,7.10)*	< 0.001*
Number of days of acute care in 2 years before pregnancy,				
0	270	38 (14.1)	Ref	
1-30	65	18 (27.7)	2.34 (1.22,4.48)*	0.010*
31-60	46	8 (17.4)	1.28 (0.56,2.97)[a]	0.558*
61 +	73	19 (26.0)	2.15 (1.15,4.02)	0.017
Linear association	*454*	*83 (18.3)*	*1.01 (1.00,1.02)**	*0.091*
Number of acute admissions in 2 years before pregnancy				
0	270	38 (14.1)	Ref	
1	121	25 (20.7)	1.59 (0.91,2.79)	0.107
2	39	11 (28.2)	2.40 (1.10,5.26)*	0.029*
> 2	24	9 (37.5)	3.67 (1.47,9.25)*	0.005*
Linear association	*454*	*83 (18.3)*	*1.55 (1.20,2.01)**	*< 0.001**
MHA[a] **2 years before pregnancy**[b]	77	16 (20.8)	1.18 (0.61,2.28)	0.663
Time since last admission (years)				
Not in 2 years before pregnancy	270	38 (14.1)	Ref	
< 1 year	99	30 (30.3)	2.66 (1.53,4.63)	0.001*
1–2 years	85	15 (17.7)	1.31 (0.68,2.52)	0.425
Family history of mental illness[b]	199	40 (20.1)	1.23 (0.74,2.04)	0.432
Medication change 1st trimester				
Continued/no stop or switch	173	25 (14.5)	Ref	
Stopped and/or Switched	118	25 (21.2)	1.66 (0.85,3.26)	0.140
No medication	163	33 (20.3)	1.60 (0.84,3.06)	0.153
Deprivation score (per unit increase), (n = 436)			1.02 (0.99,1.04)	0.147
Maternal age at delivery (per year increase), (n = 454)			0.96 (0.92,1.01)	0.091
Highest HoNOS total adjusted score in 2 years before pregnancy (per unit increase), n = 242			1.01 (0.97,1.06)	0.599

[a] Detained under section 2 or 3 of the Mental Health Act; *p < 0.05.
[b] For partner during pregnancy, victim of child/domestic abuse, smoking/harmful substance use, MHA admission and family history of mental illness variables, the reference group was 'no' and 'absent information' combined.

Table 3
Multivariable analysis of predictors of relapse in pregnancy.

	Relapse in pregnancy, odds ratios (95% CI); N = 454, n = 83 relapses		Relapse in 2nd or 3rd trimester, odds ratios (95% CI); N = 428, n = 57 relapses	
	Unadjusted	Fully adjusted	Unadjusted	Fully adjusted
Medication				
Continuation	Ref	Ref	Ref	Ref
Stopped/switched	1.66 (0.85,3.26), 0.140	1.30 (0.66,2.58), 0.446	1.41 (0.67,2.95), 0.363	1.16 (0.55,2.45), 0.703
No medication	1.60 (0.84,3.06), 0.153	**1.99 (1.05,3.75), 0.034**	1.01 (0.49,2.09), 0.977	1.43 (0.69,2.98), 0.335
Number of admissions in last 2 years	**1.55 (1.20,2.01), 0.001**	**1.37 (1.03,1.84), 0.033**	**1.68 (1.26,2.23), < 0.001**	**1.49 (1.08,2.05),0.015**
Non-affective diagnosis at baseline	**2.58 (1.45,4.58), 0.001**	**2.03 (1.16,3.54), 0.013**	**2.55 (1.35,4.81),0.004**	**2.06 (1.08,3.94),0.028**
Self-harm in last 2 years	**3.60 (1.83,7.10), < 0.001**	**2.24 (1.15,4.34), 0.017**	**3.25 (1.38,7.66),0.007**	1.87 (0.87,4.03), 0.109
Harmful Substance use	**3.37 (1.82,6.21), < 0.001**	**2.15 (1.13,4.08), 0.019**	**2.83 (1.37,5.83),0.005**	1.59 (0.74,3.41), 0.231
Smoking in pregnancy	**4.47 (2.23,8.99), < 0.001**	**2.52 (1.26,5.02), 0.009**	**4.11 (1.83,9.22), 0.001**	**2.72 (1.21,6.09), 0.015**
Ethnicity				
White	Ref	Ref	Ref	Ref
Black	**2.50 (1.24,5.04), 0.010**	**2.37 (1.23,4.57), 0.010**	**2.92 (1.31,6.50), 0.009**	**2.79 (1.26,6.18), 0.014**
Mixed/Other	**2.31 (1.01,5.25), 0.047**	**2.94 (1.32,6.56), 0.008**	**2.65 (1.04,6.77), 0.042**	**3.29 (1.27,8.53), 0.014**

Based on predictors with p < 0.2 from bivariate analysis. Maternal age at delivery, deprivation score and domestic abuse were removed from the final model as they had a fully adjusted p > 0.5.

Table 4
Sensitivity analyses to investigate stopping medication in 1st trimester.

	Excluding pregnancies with only a switch in medication, odds ratios (95% CI); N = 436, n = 79 relapses		Stopping medication abruptly (excluding only switchers and gradual stoppers), odds ratios (95% CI); N = 422, n = 75 relapses	
	Unadjusted	Fully adjusted	Unadjusted	Fully adjusted
Medication				
Continued	Ref	Ref	Ref	Ref
Stopped	1.65 (0.81,3.37), 0.170	1.30 (0.63,2.68), 0.475	1.48 (0.70,3.11), 0.302	1.16 (0.53,2.53), 0.704
No medication at start	1.61 (0.84,3.10), 0.152	**1.99 (1.03,3.84), 0.040**	1.62 (0.85,3.11), 0.146	**2.09 (1.06,4.13), 0.033**
Number of admissions in 2 years before	**1.52 (1.16,2.00), 0.003**	**1.39 (1.03,1.88), 0.034**	**1.52 (1.16,2.00), 0.003**	**1.40 (1.02,1.93), 0.038**
Baseline diagnosis	**2.56 (1.41,4.63), 0.002**	**1.99 (1.12,3.53), 0.019**	**2.56 (1.41,4.63), 0.002**	**2.01 (1.10,3.68), 0.023**
Self-harm in 2 years before pregnancy	**3.01 (1.49,6.08), 0.002**	**2.12 (1.05,4.28), 0.039**	**3.01 (1.49,6.08), 0.002**	**2.08 (1.00,4.35), 0.051**
Harmful substance use	**2.95 (1.57,5.54), 0.001**	**2.01 (1.02,3.95), 0.042**	**2.95 (1.57,5.54), 0.001**	1.97 (0.96,4.03), 0.063
Smoking	**4.28 (2.06,8.89), < 0.001**	**2.44 (1.16,5.10), 0.018**	**4.28 (2.06,8.89), < 0.001**	**2.75 (1.24,6.09), 0.012**
Ethnicity				
White	Ref	Ref	Ref	Ref
Black	**3.16 (1.43,6.98), 0.022**	**2.54 (1.20,5.38), 0.015**	**4.18 (1.72,10.19),0.002**	**3.40 (1.45,8.00), 0.005**
Mixed/Other	**2.84 (1.16,6.96), 0.005**	**3.12 (1.33,7.35), 0.009**	**3.52 (1.33,9.34), 0.012**	**4.21 (1.61,11.00),0.003**

Based on predictors with $p < 0.2$ from bivariate analysis. Maternal age at delivery, deprivation score and domestic abuse were removed from the final model as they had a fully adjusted $p > 0.5$.

unadjusted difference between continuing vs. stopping/switching medication, but multivariable output remained similar (Supplementary Table 5). Exclusion of 14 pregnancies which ended in 2nd trimester made no difference (Supplementary Table 6). There was no association between these early ending pregnancies and relapse (Fisher's exact, $p = 0.482$). Women who stopped an antipsychotic had higher odds of relapse than women who continued/switched, but this was not the case for mood stabilisers or antidepressants. However these findings were not significant (Supplementary Table 7).

4. Discussion

In 389 women with SMI, there were 83 (18.3%) relapses during 454 pregnancies – 58 (24.4%) in pregnancies of women with non-affective diagnoses and 25 (11.6%) in women with affective disorders. Based on multivariable analyses, the nature and severity of the mental disorder (non-affective psychosis at baseline, recent admissions, harmful substance use, and recent self-harm) was associated with relapse in pregnancy. Smoking and non-white ethnicity also independently predicted relapse. Continuing medication compared with not taking medication at the beginning of pregnancy was protective, but we were unable to draw conclusions about switching or stopping medication in the first trimester.

These findings provide some reassurance that although relapse can occur in pregnancy, most women in this cohort did not have episodes needing acute care or manifesting as self-harm. Our findings suggest that risk of relapse in women with bipolar disorder may be lower than in studies of women attending specialist clinics (Viguera et al, 2007, 2011), and comparable with the few studies carried out on more representative samples (Judd et al., 2014). There are few data in women with non-affective psychoses. One other large study to date, which used administrative data, found that 24% of pregnant women with schizophrenia were admitted or visited a mental health emergency service, which is comparable to our findings (Vigod et al., 2014).

There has been little previous research into risk factors for relapse of severe mental disorder in pregnancy, although associations with severity of the pre-existing psychiatric illness have been reported (Munk-Olsen et al., 2009; Vigod and Ross, 2010; Viguera et al., 2007). Using comprehensive clinical data we found that smoking, recent self-harm and substance misuse also showed associations with relapse, potentially suggesting higher-risk lifestyles. Such women may find it more difficult to prioritise stopping smoking or substance use in pregnancy; alternatively, smoking and substance misuse may be associated with worsening mental health. Both are important risk factors for adverse fetal outcomes (Stein et al., 2014), which need to be addressed by services. Being of black ethnicity was also associated with increased risk of relapse in pregnancy, consistent with research showing higher rates of relapse and worse outcomes in people of black compared with white ethnicity (Mann et al., 2014). Non-affective diagnosis has also been associated with worse outcomes in patients with psychosis (Morgan et al., 2014) as well as non-adherence to medication (Porcelli et al., 2016). Relapse or psychiatric admission in pregnancy may be an important predictor of relapse postpartum and further work with this cohort has looked at relapse in the first three months postpartum including admission in pregnancy as a predictor.

We did not find an association between medication discontinuation or switching and relapse, in contrast to others (Viguera et al., 2007) who found 86% risk in women with bipolar disorder stopping mood stabilising medication compared with 37% in women who continued, independent of disorder severity measures. Different definitions of relapse may explain some of this heterogeneity. In Viguera's study, it could not be determined whether medication change in the first trimester occurred before or after a relapse in early pregnancy; however, excluding women who relapsed in the first trimester attenuated our association, and indeed Viguera's data showed particularly high risk of relapse in early pregnancy. In observational research, independent effects of psychiatric illness and medication can be challenging to disentangle. Different classification of medication exposures may also explain some discrepancy in findings. Viguera investigated stopping mood stabilisers from 6 months before to 12 weeks after conception and excluded women who stopped medication over 6 months before. In our data women who stopped medication before pregnancy would be in the 'no medication' group and tended to relapse early.

To our knowledge, there are no comparative data in pregnant women with schizophrenia; however, outside the perinatal period, switching medication appears well tolerated (Roussidis et al., 2013). These clinical records enabled us to investigate potential impact of other moderators, notably DV. This needs replication in larger samples but its potential adverse impact on mental health is reported elsewhere (Khalifeh et al., 2015) as is the importance of addressing DV perinatally (NICE, 2014).

A major strength of this study was the novel methodology using electronic secondary mental health data. This allowed investigation of a larger cohort of women than previous clinical studies, with more detail on illness severity and other psychosocial characteristics than population registries. SLaM provides near-monopoly secondary mental health

services to its catchment, so these data are likely to include most pregnant women with SMI in this locality. The linkage with HES enabled us to collect psychiatric admissions data covering England, minimising loss to follow-up and giving a full picture of illness history for this dynamic cohort. We were also able to collect data on recorded DV, substance use and self-harm. Detailed clinical data on medication enabled us to capture changes resulting from mutual decisions made under clinical guidance (Swanson et al., 2015) or self-initiated cessation decisions, as well as recorded adherence, so we were able to address some misclassifications not achievable with registry data. CRIS data are not collected for research and rely on accuracy and comprehensiveness of clinical note keeping. Although we used multiple validated search terms, some information may be absent or underreported, such as that on smoking. We were not able to ascertain previous history of perinatal episodes which have been shown predictive of postpartum relapse. However, this methodology enabled us to observe this high-risk group of pregnant women in a real-world setting. We were able to include self-harm and women potentially more severely at risk than may take part in clinical studies.

Considering sample selection, our data source does not include women managed only in primary care. However, the threshold for referral to secondary care may be lower in pregnancy, and national guidelines (NICE, 2014) recommend referral of pregnant women with SMI history to secondary mental health care. There may also be selection into pregnancy in women with SMI, since reported fertility is lower than that in the general population (Howard et al., 2002; Vigod et al., 2012). Schizophrenia may affect relationship stability (Howard, 2005) and there are also reported higher rates of termination (Laursen and Munk-Olsen, 2010) and unplanned pregnancies in women with SMI (Miller and Finnerty, 1996). These factors affect comparability with times outside pregnancy. The linkage to HES data allowed a robust method of identifying pregnancies, covering deliveries across England. Home births are thought to be under recorded in HES (2.4% of deliveries in England in 2011 were at home) (ONS, 2013) though pregnancies in women with SMI are considered high-risk obstetrically so home births may be less likely. The retrospective design may have identified a particularly severe group of women since by default women admitted in pregnancy would have been included in the cohort. Women also receive many diagnoses in the health records; therefore, potential misclassification may have affected inclusion.

Considering the outcome, admission to acute care may not be a sensitive indicator of relapse, as less severe relapses may be managed by the secondary services already providing care, or by medication changes. Whilst using this endpoint may have missed some cases of relapse, it may also have included women admitted for social reasons, thus reflecting socio-economic disadvantage rather than relapse *per se*. However, all admissions to the MBU during pregnancy were for acute illness so this is unlikely to have skewed the results significantly. We did not carry out survival analyses as dates of admission were considered to be insufficiently accurate estimates of end-point timing.

Considering exposures, the stopped/switched medication group may be heterogeneous in terms of reasons for stopping/switching. However most women who stopped medication in the first trimester did so because of pregnancy (Taylor et al., 2015) and sensitivity analyses excluding switchers and gradual stoppers made little difference to findings. We did not have the power to analyse gradual stoppers separately and there may have been some misclassification of speed of stopping medication as it was difficult to determine from the clinical notes and we assumed abrupt stopping unless stated otherwise. Previous research has shown that women with bipolar disorder may have higher risk of relapse if they discontinue or do not take medication. Women with non-affective psychosis may not be the same. However we did not have a large enough sample to ascertain predictors or moderators of relapse separately in the non-affective and affective groups. The fairly small proportion of relapses detected limited statistical power to detect some associations, and larger cohorts would be needed to address some remaining questions. Prospective clinical research could address some of the issues of unrecorded clinical information although assembling a large cohort would be costly and time-consuming with higher risk of attrition bias.

5. Conclusions

Women with indicators of more severe SMI are more likely to relapse in pregnancy, these indicators include having more admissions in the two years prior to pregnancy, non-affective illness, history of self-harm, smoking and substance use. We found weaker evidence of association with medication change but women on no medication at the start of pregnancy were more likely to relapse in early pregnancy. While the risks and benefits of taking medication in pregnancy must be weighed up for each individual (NICE, 2014) this study has identified those at particularly high risk of relapse in pregnancy – evidence that could be shared with women who are making decisions about medication in pregnancy. Women with SMI have multiple risk factors for adverse pregnancy outcomes including risk of relapse, smoking, substance use, medication and should be under care of specialist services during pregnancy. Attention should also be paid to potentially modifiable risk factors including smoking and substance use.

Financial support

LMH and CT are supported by an NIHR Research Professorship (NIHR-RP-R3-12-011). RS & MB are part-funded by the National Institute for Health Research Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. This study has been part-funded by the Johnson & Johnson CSR Citizenship Trust. Johnson & Johnson had no involvement in the design of the study, or access to any data throughout the project. This research was also supported by the Biomedical Research Nucleus data management and informatics facility at South London and Maudsley NHS Foundation Trust, which is funded by the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London and a joint infrastructure grant from Guy's and St Thomas' Charity and the Maudsley Charity.

Conflicts of interest

RS and MB have received research funding from Pfizer, Janssen, Lundbeck and Roche. RS supervises a PhD student funded by GSK.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpsychires.2018.06.019.

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