Rapid repeat pregnancy in women with schizophrenia

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A B S T R A C T

Aim: Women with schizophrenia are vulnerable to adverse reproductive health outcomes. Short inter-pregnancy interval, or rapid repeat pregnancy, is associated with maternal and infant complications, and may be preventable. Whether women with schizophrenia are at disproportionate risk for rapid repeat pregnancy is unknown.

Methods: This population-based cohort study in Ontario, Canada (2002–2013) compared women with and without schizophrenia on their risk of rapid repeat pregnancy, defined as pregnancy within 12 months of an index live birth. Among women with public drug coverage, those with and without schizophrenia were compared on their use of non-barrier contraception (hormonal and surgical) post-delivery.

Results: Women with schizophrenia (n = 1565) were at higher risk for rapid repeat pregnancy than women without schizophrenia (n = 924,657) (6.3% vs. 3.9%, adjusted relative risk, aRR 1.31, 95% confidence interval, CI, 1.07–1.59). They had more rapid repeat pregnancies resulting in live births (aRR 1.85, 95% CI 1.26–2.72), but not pregnancy losses (aRR 1.50, 95% CI 0.99–2.29) or induced abortions (aRR 1.07, 95% CI 0.81–1.42). Post-delivery non-barrier contraception use was similar between groups (43.7% vs. 43.6%, aRR 1.06, 95% CI 0.93–1.20), although women with schizophrenia were more likely to use injectable contraception (14.1% vs. 10.1%, aRR 1.67, 95% CI 1.35–2.07).

Discussion: Women with schizophrenia are at higher risk than their peers for rapid repeat pregnancy, but use non-barrier contraception at similar rates. The postnatal period is an opportune time to initiate targeted interventions designed to optimize planning for any future pregnancies, and contribute to improving maternal and child health in this vulnerable group.

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1. Introduction

Schizophrenia, a chronic and serious mental illness for most who suffer from it, affects around 1% of the population (Janoutova et al., 2016). Women with schizophrenia have traditionally had lower birth rates than unaffected women (Vigod et al., 2012). In recent years, possibly related to decreased institutionalization, and the increase in early intervention psychosis programs and fertility-sparing second generation antipsychotic medications as a mainstay of treatment, women with schizophrenia have had more opportunities to become mothers (Solari et al., 2009). A population-based study showed fertility rates increased among young women with schizophrenia aged 20–24 to the point that by 2009, their birth rates were comparable to those of their unaffected counterparts (Vigod et al., 2012). This suggests that pregnancy outcomes in this group warrant close attention. Unfortunately, recent population-based studies show that women with schizophrenia are more likely to experience adverse pregnancy outcomes than unaffected women, including increased rates of hypertensive disorders of pregnancy, as well as preterm birth and infants born at extremes of weight for gestational age that place infants at increased risk for various chronic medical and mental health problems across the lifespan (Heun-Johnson et al., 2019; Jones et al., 2014; Simoila et al., 2019; Vigod et al., 2014).

Rapid repeat pregnancy (RRP) generally defined as a short inter-pregnancy interval where a second pregnancy occurs within

12–24 months of a previous birth, is associated with increased risk for many of the complications noted above (Conde-Agudelo et al., 2006; Kwon et al., 2012). Public health and other clinical service interventions to prevent RRP in groups at high risk for RRP such as adolescents and women from socio-economically disadvantaged backgrounds can successfully reduce risk for this outcome (Lewis et al., 2012; Norton et al., 2017). This suggests that if women with schizophrenia are at high risk for RRP, it could be a target for intervention to improve their pregnancy outcomes. Women with schizophrenia share many of the same vulnerabilities for RRP as other high-risk populations (i.e. they are more likely to engage in unprotected sex, to be victims of sexual violence and to have unintended pregnancies than unaffected women) (Taylor et al., 2015; Seeman and Ross, 2011; Oliver, 2013). Whether they are specifically at increased risk for RRP is unknown.

In a population-based cohort of Canadian women with a live-born infant between 2002 and 2013, we compared the risk for rapid repeat pregnancy in women with versus without schizophrenia. To add context to the findings, we also compared the use of hormonal and surgical contraception within 12 months of the index birth between the same two groups in a subset of the sample who were eligible for public drug coverage.

2. Methods

2.1. Study design and setting

This was a population-based cohort study that used linked health administrative data from Ontario, Canada's largest province (population ~13.5 million) to compare women with schizophrenia to those without schizophrenia on their rates of rapid repeat pregnancy and use of contraception following a live birth in 2002 to 2013. Ontario has a public health insurance plan in which medically necessary hospital and physician services are provided free of charge to residents.

2.2. Data sources

Data were obtained from ICES (www.ices.on.ca), a non-profit healthcare evaluation research institute where Ontario sociodemographic and health service use data are linked using a unique anonymous identifier for all Ontario residents with a valid health card (Williams et al., 1996). Ontario's Registered Persons Database (RPDB) was used for maternal and infant birth date, postal code, and date of death, and to link study participants across the other datasets, including (1) the Ontario Health Insurance Plan (OHIP) database for physician billings; (2) the National Ambulatory Care Reporting System (NARCS) for emergency department data; (3) the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) for non-mental health hospitalization data, which also includes a MOMBABY dataset that allows for linkage of these data between mothers and infants and includes information on pregnancy outcome, including livebirth or stillbirth; and (4) the Ontario Mental Health Reporting System (OMHRS) for detailed data on psychiatric hospitalizations. These databases have been shown to be complete and reliable with respect to primary diagnostic, prescription, and procedure information (Muldoon et al., 2013). For access to information on prescribed hormonal contraception, we used the Ontario Drug Database (ODB) that contains accurate information on dispensed prescription medication for individuals for whom public drug coverage is provided because they receive social assistance (Levy et al., 2003).

2.3. Participants

The cohort comprised all Ontario women aged 18–49 years with a live birth between April 1, 2002 and March 31, 2013. The index birth was identified using the MOMBABY dataset, which identifies >98.0% of Ontario births. Women with intellectual and developmental disabilities (IDD) were not included because of the dual vulnerability for rapid repeat pregnancy associated with the additional diagnosis of IDD (Brown et al., 2018a; Brown et al., 2018b). A sub-cohort for the contraception analyses included only women covered under the ODB. Women with schizophrenia were identified using an algorithm requiring one hospitalization or at least two outpatient visits with a diagnosis of schizophrenia, schizoaffective disorder, or psychotic disorder not otherwise specified in the two-year period prior to the index birth (Kurdyak et al., 2015).

2.4. Outcomes

The primary outcome (rapid repeat pregnancy) was a composite of a live birth, pregnancy loss (stillbirth ≥20 weeks gestation or spontaneous abortion <20 weeks gestation), or induced abortion occurring within 3 to 12 months of the index livebirth. The time between 0 and 3 months after the index live birth was not included in the outcome window because pregnancy codes during this initial post-delivery time could relate to the index live birth (Table S1). Live births, stillbirths, and induced abortions are all captured accurately in the ICES inpatient and outpatient datasets; early spontaneous abortions that do not come to medical attention are not captured (Canadian Institute for Health Information, 2014; Statistics Canada, 2006). Although the adverse effects associated with spacing of pregnancies >12 months apart are not as high as for those <12 months apart, and it has been recommended that the World Health Organization no longer label 24-month inter-pregnancy intervals as short, we also examined repeat pregnancies from 3 to 24 months after the index birth to contextualize the findings (Shachar and Lyell, 2012).

Contraception, measured in the 0–12 months following the index live birth, was a composite outcome of hormonal and surgical contraception. Hormonal contraception comprised oral contraceptive pill prescription dispensations, injectable contraceptive (depot medroxyprogesterone acetate [DMPA]), and intrauterine devices. Surgical contraception comprised sterilization (tubal ligation or sterilization implant) and hysterectomy (Table S2). Use of barrier contraction was not measurable in the health administrative datasets.

2.5. Covariates

Covariates considered were: age, parity, rural residence (<10,000 residents), neighbourhood income quintile, stable and unstable chronic medical conditions, substance or alcohol use disorder diagnosis, and continuity of care with a primary care provider, all measured either at the time of the index delivery or in the two years prior to that date. Chronic medical conditions were measured using the collapsed ambulatory diagnostic groups from the Johns Hopkins Clinical Groups System, and categorized as stable or unstable (University, 2010). Continuity of primary care was measured by the Usual Provider Continuity (UPC) Index, calculated by dividing the number of visits made to the usual primary care provider (e.g., family physician) by the total number of visits to all primary care providers in the two years before the index live birth (Jee and Cabana, 2006).

2.6. Analysis

Baseline characteristics were described using frequencies and proportions for women with and without schizophrenia. In the overall sample, an unadjusted modified Poisson regression model was constructed to compare risk for the primary composite RRP outcome and each of its individual elements among women with versus without schizophrenia, generating a relative risk (RR) and 95% confidence interval (CI) (Zou, 2004). Models were then adjusted for age and parity at index delivery, neighbourhood income quintile, rurality, presence of chronic medical conditions, and

continuity of primary care. Among participants eligible for public drug coverage, the above analysis was conducted with the composite outcome of any contraception, then for any hormonal, any surgical, and each specific type of hormonal contraception.

In additional analyses for both the RRP and contraception outcomes, we restricted the cohort to primiparous women, as this may be a particularly ideal target population to engage in postpartum reproductive health programs.

Analyses were conducted using SAS v9.2. The study was exempt from research ethics approvals, and was approved by the ICES privacy office (ICES 2014-0900-522-000).

3. Results

3.1. Participant characteristics

There were 1565 women with schizophrenia and 924,657 women without who had at least one live birth during the study period. Compared to women without schizophrenia, women with schizophrenia were younger (6.2% age 18–19 years, vs. 3.6%), lower income (38.7% in the lowest income quintile, vs. 21.3%), had more stable (41.1% vs. 27.3%) and unstable chronic medical conditions (24.2% vs. 13.2%), had higher rates of substance use disorders (27.0% vs. 2.1%), and had lower continuity of primary care (37.7% lowest UPC vs. 21.1%) (Table 1). The sub-cohort with public drug coverage comprised 609 (38.9%) of the women with schizophrenia in the original cohort, and 34,650 women without schizophrenia (3.7%). In this sub-cohort, half of women were in the lowest income quintile, and tended to have overall higher rates of morbidity than women in the overall cohort (also in Table 1). Observed patterns in terms of differences in baseline characteristics between women with and without schizophrenia were very similar to what was observed in the larger cohort.

3.2. Rapid repeat pregnancy

Overall, 99 (6.3%) women with schizophrenia had a repeat pregnancy within 12 months, compared to 36,065 (3.9%) without schizophrenia (RR 1.62, 95% CI 1.33–1.98; aRR 1.31, 95% CI 1.07–1.59) (Table 2). This association was largely driven by a statistically significant increased risk of a repeat live birth (aRR 1.85, 95% CI 1.26–2.72). The risk for a pregnancy loss in the 12 months

post-delivery was not statistically significantly elevated after co-variate adjustment (aRR 1.50, 95% CI 0.99–2.29). Risk for induced abortion was similar between groups (aRR 1.07, 95% CI 0.81–1.42). Among primiparous women, the risk of rapid repeat pregnancy was also elevated in women with schizophrenia versus those without (6.1% vs. 3.9%, aRR 1.28, 95% 1.01–1.62) (Table S3). More than 1 in 5 women in both groups had a repeat pregnancy within 24 months of the index birth, and there was no difference between groups overall, or for any pregnancy outcome (Table S4).

3.3. Contraception

Overall, a form of hormonal or surgical contraception was used by 266 (43.7%) women with schizophrenia and 15,112 (43.6%) women without schizophrenia in the 12 months after delivery (aRR 1.06, 95% CI 0.93–1.20). Only injectable contraception was used more commonly in women with schizophrenia (14.1% vs. 10.1%, aRR 1.67, 95% CI 1.35–2.07); there were no differences between groups for any of the other hormonal or surgical contraception methods studied (Fig. 1). In primiparous women, there were no differences between women with and without schizophrenia in the use of hormonal or surgical contraception (Table S5).

4. Discussion

In this population-based study, about 1 in 16 women with schizophrenia with a live-born infant were pregnant again within a year post-birth – a rate almost twice as high as in their counterparts unaffected by schizophrenia. This increased risk did not extend when considering births occurring within 24 months from delivery, a less risky inter-pregnancy interval. In the 12 months from the index delivery, fewer than half of the women with schizophrenia in our cohort used hormonal or surgical contraception, and the rate of injectable contraception use was 14%, only slightly higher than that among unaffected women. Taken together, these results suggest that there is room for improvement in the post-delivery reproductive care of women of schizophrenia to provide education about the risks of RRP and optimize planning for any future pregnancies. Since women are by necessity in contact with the health care system around the time of a first delivery, an opportune moment exists to intervene successfully.

Table 1
Baseline characteristics of women with schizophrenia and without schizophrenia at the time of the index live birth for the overall cohort, presented as n (%) unless otherwise specified.

Variable	Full cohort		Cohort with public drug coverage	
	Schizophrenia (N = 1565)	No schizophrenia (N = 924,657)	Schizophrenia (N = 609)	No schizophrenia (N = 34,650)
Age				
18–19 years	97 (6.2)	33,020 (3.6)	39 (6.4)	4715 (13.6)
20–34 years	1138 (72.7)	712,574 (77.1)	453 (74.4)	24,781 (71.5)
35–49 years	330 (21.1)	179,063 (19.4)	117 (19.2)	5154 (14.9)
Primiparous (index pregnancy)	1174 (75.0)	701,074 (75.8)	453 (74.4)	21,635 (62.4)
Income quintile (Q)				
Q1 (lowest)	602 (38.7)	195,926 (21.3)	304 (50.2)	17,408 (50.4)
Q2	348 (22.4)	182,149 (19.8)	119 (19.6)	7554 (21.9)
Q3	239 (15.4)	187,577 (20.3)	82 (131.5)	4600 (13.3)
Q4	209 (13.4)	193,421 (21.0)	62 (10.2)	3140 (9.1)
Q5 (highest)	157 (10.1)	162,055 (17.6)	39 (6.4)	1841 (5.3)
Rural residence (<10,000)	122 (7.8)	88,439 (9.6)	42 (6.9)	3131 (9.0)
Chronic medical condition				
Stable	643 (41.1)	252,664 (27.3)	284 (46.6)	13,018 (37.6)
Unstable	378 (24.2)	122,245 (13.2)	167 (27.4)	7553 (21.8)
Substance use disorder	423 (27.0)	18,992 (2.1)	226 (37.1)	3398 (9.8)
Usual care provider index				
Low	583 (37.3)	195,382 (21.1)	254 (41.7)	11,123 (32.1)
Moderate	590 (37.7)	332,441 (36.0)	220 (36.1)	12,689 (36.6)
High	368 (23.5)	350,434 (37.9)	127 (20.9)	9693 (28.0)
Fewer than 3 visits	24 (1.5)	46,300 (5.0)	8 (1.3)	1145 (3.3)

Table 2
Rapid repeat pregnancy within 1 year from a live birth for 1565 women with schizophrenia, compared to 924,657 women without schizophrenia. Presented as relative risks (RR) and 95% confidence intervals (CI).

Outcome	Group	N (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)[a]
Rapid repeat pregnancy	*Schizophrenia*	99 (6.3)	1.62 (1.33–1.98)	1.31 (1.07–1.59)
	No Schizophrenia	36,065 (3.9)	1.00 (Reference)	1.00 (Reference)
Live birth	*Schizophrenia*	26 (1.7)	2.20 (1.50–3.23)	1.85 (1.26–2.72)
	No Schizophrenia	6983 (0.8)	1.00 (Reference)	1.00 (Reference)
Pregnancy loss	*Schizophrenia*	23 (1.5)	1.74 (1.16–2.63)	1.50 (0.99–2.29)
	No Schizophrenia	7773 (0.8)	1.00 (Reference)	1.00 (Reference)
Induced abortions	*Schizophrenia*	50 (3.2)	1.39 (1.05–1.83)	1.07 (0.81–1.42)
	No Schizophrenia	21,309 (2.3)	1.00 (Reference)	1.00 (Reference)

[a] Adjusted for age, parity an index delivery, neighbourhood income quintile, rural vs. urban residence, and stable and unstable chronic medical conditions, and continuity of primary care.

4.1. Context within current literature

To our knowledge, RRP has not been studied in relation to schizophrenia. However, our results are consistent with a U.S. study in a predominately African American sample where 5.6% of women ages 15–36 years with moderate to severe depression were at increased risk of repeat pregnancy within six months of a first birth (Patchen and Lanzi, 2013). Brown et al. (2018b) found that women with intellectual and developmental disabilities had a higher rate of rapid repeat pregnancy compared to unaffected women, also of a similar rate and relative rate to that observed in the current study (7.6% versus 3.9%, aRR 1.34, 95% CI 1.18–1.54). More data are available in the contraception literature. Therein, barrier methods are used less frequently among women with schizophrenia and contraceptive pill adherence is lower than among unaffected women, especially in the setting of a comorbid substance use disorder (Callegari et al., 2015; Seeman and Ross, 2011; Simoila et al., 2018). Our inability to measure the use of barrier contraception could explain the difference between our findings and those of previous studies.

4.2. Potential explanations for findings

One explanation for the current findings could be that women with schizophrenia are at high risk for unplanned pregnancy. Women with schizophrenia are socially vulnerable, are at high risk for sexual assault, and have high rates of comorbid substance use disorders, each of which could lead to unplanned pregnancy (Miller and Finnerty, 1996; Connery et al., 2014; Nesvag et al., 2015). Schizophrenia is also associated with impaired cognitive processing, social deficits, and abnormalities in perception of reality that could lead to difficulty in planning and asserting for the use of contraception during intimacy or inconsistent adherence to contraceptive methods, even in planned and consensual sexual encounters (Abel and Rees, 2010; Seeman and Ross, 2011). Fewer than 50% of women with schizophrenia in the current study received any form of hormonal or surgical contraception in the 1 year post-delivery, so if they were unlikely to use barrier contraception, this could contribute to a higher risk for RRP.

Interestingly, the difference in RRP rate was driven mainly by a higher rate of repeat live births. This could be explained by the fact that women with schizophrenia might not realize that they are pregnant until late in pregnancy when induced abortion is no longer an option (Seeman, 2013). However, it may be important to consider that this might reflect that some rapid second pregnancies may be intentional. Among adolescent mothers, more than half report idealizing pregnancy as a significant and positive life event in their life (Quinlivan, 2004). In fact, subsequent teen pregnancies are more likely to be intended than first teen pregnancies (Coleman and Cater, 2006; Seamark, 2001). Women with psychotic disorders are at a higher risk
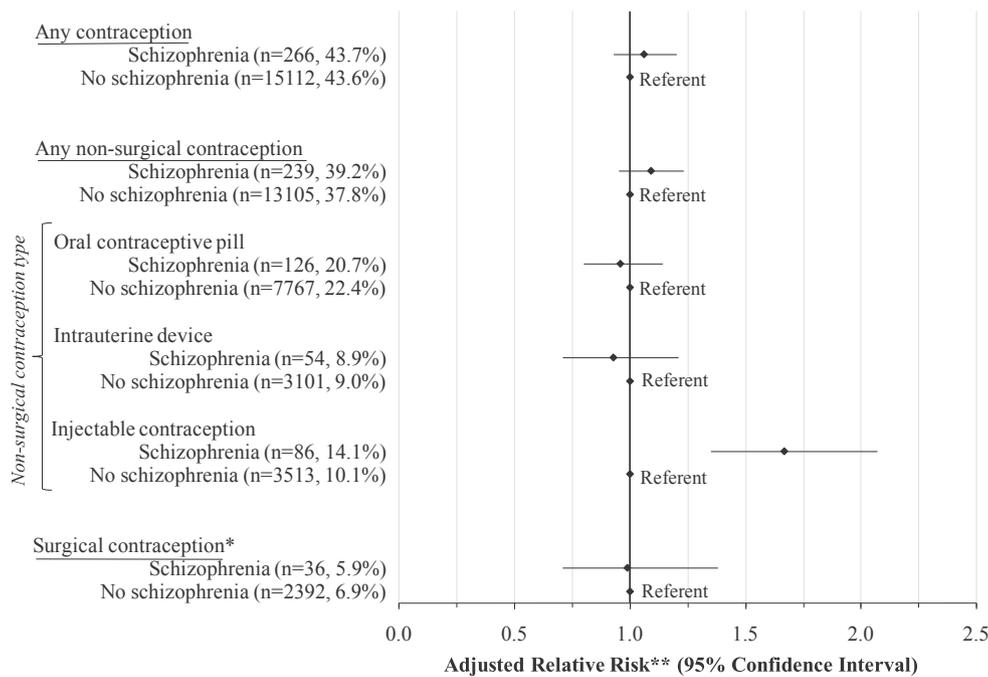

Fig. 1. Contraception within 1 year from a live birth for 609 women with schizophrenia compared to 34,650 women without schizophrenia (referent). Presented as adjusted relative risks and 95% confidence intervals. *Hysterectomy, tubal ligation, or sterilization implant. **Adjusted for age, parity an index delivery, neighbourhood income quintile, rural vs. urban residence, and stable and unstable chronic medical conditions, and continuity of primary care.

compared to unaffected women of losing custody of their children to social services (Vigod et al., 2018). It is possible that rapid repeat pregnancy in this group could represent intentional repeat pregnancy and another opportunity at motherhood (Broadhurst et al., 2015). Given the relative safety of injectable hormonal contraception and its potential advantages in the schizophrenia population, its low absolute rate of use in this group could be explained by such a lack of desire to prevent pregnancy. These low rates of injectable contraception use could also reflect a broader lack of a systematic approach to contraceptive counselling for women with schizophrenia and the minimal focus on their reproductive health in clinical guidelines and programming (Bakry et al., 2008; Judd and Newman, 2017).

4.3. Potential implications

Rapid repeat pregnancy is an undesirable outcome due to the maternal and child risks linked to a small inter-pregnancy interval (Conde-Agudelo et al., 2006). The potential health implications of RRP could be even greater among women with schizophrenia, given their baseline risk for medical comorbidity (including obesity, diabetes and cardiovascular disease), elevated rates of smoking, alcohol and substance dependence, and intimate partner violence, and other issues that increase risk for pregnancy complications (Brameld et al., 2017; Goodwin et al., 2007; Trevillion et al., 2012). Further, short pregnancy intervals may not allow time for adequate planning and management in the setting of these problems. Women with schizophrenia may also face parenting challenges due to their illness or or other socioeconomic disadvantages (e.g. low income, less likely to have partner) that could be compounded with having two young dependents. While some women with schizophrenia may intentionally want to become pregnant again in the setting of custody loss, it is important to consider a succession of pregnancies followed by custody losses can be both devastating and destabilizing to mental health (Dolman et al., 2013). Therefore, efforts to reduce RRP rates are likely warranted.

While there is no evidence to date on interventions to target RRP among women with schizophrenia, integrated preconception programs that have been shown to prevent rapid repeat pregnancy in other high-risk populations (e.g., adolescents) may be amenable to modification for women with schizophrenia (Patchen et al., 2013). These programs include contraception service models with proactive monitoring of contraceptive use, as well as inclusion of partners and families in contraception education (Norton et al., 2017). Effective programs emphasize *planning* the next pregnancy rather than *avoiding* an "unintended" pregnancy, and promote individual goal setting using motivational interviewing approaches to help a woman progress on her readiness to change in relation to complex health behaviours (Barnet et al., 2009; Dean et al., 2014; Gray et al., 2006; Sebastian et al., 2012; Stevens et al., 2017). This may be a particularly helpful approach for women with schizophrenia who desire to replace a child lost from their custody and who therefore do not wish to use contraception for the sole purpose of preventing a pregnancy (i.e. shifting the frame to focus on planning for a more healthy future pregnancy could be a more successful approach). Personalized, non-judgmental approaches that incorporate continuous monitoring and check-in (rather than traditional one-off sexual health education interventions), may be particularly useful in the context of the social and cognitive vulnerability of a new mother with schizophrenia. It may also be important to consider embedding reproductive planning within existing mental health services for schizophrenia where the mental health team often acts as a primary care team, coordinating care and ensuring appropriate and timely access to key medical services.

4.4. Limitations

This study focused on RRP after live births specifically, so the findings do not necessarily pertain to women with schizophrenia more broadly who have had non-live birth outcomes such as spontaneous or therapeutic abortions, or stillbirth. Further limitations are common to all studies using health administrative data. First, while we used a validated algorithm to classify schizophrenia, some women could have been misclassified, biasing the results toward not finding an effect. Similarly, though we identified repeat pregnancies that came to the attention of the healthcare system, we could have missed pregnancies ending in early spontaneous abortion that did not require medical intervention. While we were able to account for some potential confounders (e.g., age, socioeconomic status), not all covariates of interest were available (e.g. data on race, ethnicity or immigration status; population-level child apprehension and medication data). Some variables, such as substance use disorders, were so much more common in the schizophrenia group that they could not be included in the multivariable models for adjustment. Finally, we were unable to examine barrier methods of birth control or adherence rates to prescribed contraceptive methods.

5. Conclusions

Women with schizophrenia have higher rates of rapid repeat pregnancy than unaffected women, and similar rates of hormonal and surgical contraception. An initial delivery is an opportune time to intervene to optimize planning for future pregnancies, so future research to understand the key drivers of RRP in this group (e.g. sociodemographic factors, mental status indicators, substance and alcohol use, and health service connectivity) is warranted to guide program development for this uniquely vulnerable population.

are those of the author and not necessarily those of CIHI. The dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the programs may rely upon coding templates or macros that are unique to ICES.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.08.007.

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