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Title: Antidepressant Use in Late Gestation and Breastfeeding Rates at Discharge from Hospital

Well Established

The choice to breastfeed when taking an antidepressant poses a dilemma for some women, with previous studies suggesting that women taking antidepressants have lower rates of breastfeeding intention and initiation.

Newly Expressed

Antidepressant use is associated with a reduced likelihood of breastfeeding at discharge from hospital, but this association appears to be strongly influenced by factors such as underlying maternal psychiatric illness and perinatal outcomes including preterm birth and neonatal hospital admission.

Abstract

Background: Few studies have investigated breastfeeding outcomes among women exposed to antidepressants.

Research Aim: To evaluate the association between antidepressant use in late gestation and maternal psychiatric illness on breastfeeding rates at discharge from hospital.

Methods: Retrospective cohort study of 32,662 women delivering live-born singletons between January 2001 to December 2008. Electronic hospital records were utilised to obtain data on antidepressant exposure during late gestation and whether mothers were breastfeeding at discharge from hospital following delivery.

Results: Five hundred and seventy-five women received a dispensing for an antidepressant in late gestation (exposed), 1,552 did not receive a dispensing for an antidepressant but had a reported psychiatric illness (disease comparison) and 30,535 served as non-exposed controls. Exposed women were significantly less likely to be breastfeeding their infants at discharge from hospital compared to non-exposed women (adjusted odds ratio

[aOR] 0.63; 95%CI 0.50-0.80), but no statistically significant difference was observed when compared to women in the disease comparison group (aOR 0.83; 95%CI 0.65-1.07). In stratified analyses, compared to women in the disease comparison group, exposed women were significantly less likely to be breastfeeding their infants at discharge from hospital if their neonate was delivered at term (aOR 0.73; 95%CI 0.55-0.98), but not preterm (aOR 1.24; 95%CI 0.66-2.32).

Conclusion: While the negative association between antidepressant use and breastfeeding rates is confounded underlying maternal psychiatric illness, the association appears to differ according to neonatal outcome status. Overall, these results highlight that these women may benefit from additional education and support to improve breastfeeding rates.

Main Manuscript

Background

The benefits of breastfeeding are well established (Gartner et al., 2005; Hoddinott, Tappin, & Wright, 2008). A mother's choice to breastfeed and her success in doing so, are influenced by a range of personal, social, and environmental factors. Maternal medication use has been highlighted as a potential barrier to breastfeeding due to concern regarding infant "exposure" through breast milk (Pearlstein et al., 2006).

It is well recognised that antenatal depression and related psychiatric illnesses are significant risk factors for a range of adverse pregnancy outcomes (Bonaria et al., 2004; Ryan, Milis, & Misri, 2005). Included in this is a significant increased risk of major postpartum depressive illness, which affects up to 26.3% of women following delivery (Norhayati, Hazlina, Asrenee, Emilin, 2015). Maternal suicide has been reported as the leading cause of mortality in the first 12 months after birth in many countries (Cantwell et al., 2011) and there are case reports of infanticide in the context of maternal psychiatric illness

("Bringing postnatal depression out of the shadows", 2012). Post-partum depression and related psychiatric illnesses are increasingly recognised as causing substantial morbidity and functional impairment in the mother and long-term negative consequences for infant and child development (Kendall-Tackett, & Hale, 2010; Quevedo et al., 2012; Stein et al., 2014). The growing body of evidence on the adverse effects associated with psychiatric illnesses in the perinatal period underscores the importance of appropriate and timely treatment.

Antidepressants, particularly Selective Serotonin Reuptake Inhibitors (SSRIs) are commonly prescribed for many lactating women suffering from depression or related psychiatric illnesses (Howard et al., 2014). Despite this, few studies have investigated breastfeeding outcomes among women taking antidepressants. While the risks to the breastfed infant are considered low, the choice to breastfeed when taking an antidepressant may pose a dilemma for some women (Gorman, Kao, & Chambers, 2012). Anecdotal reports of concerns regarding infant "exposure" through breast milk may result in women taking antidepressants being less likely to breastfeed their infants. This is supported by two recent studies that demonstrated that women taking antidepressants have lower rates of breastfeeding intention and initiation (Bogen, Hanusa, Moses-Kolko, & Wisner, 2010; Gorman et al., 2012), but it is unclear what role underlying maternal illness may play.

Given serotonin plays a role as a regulator of lactation homeostasis, medications such as antidepressants, that inhibit serotonin reuptake may also disrupt the normal physiological process associated with lactation. In line with this, one study has previously demonstrated that primiparous women taking SSRIs are at a 2-fold increased risk of delayed stage II lactogenesis (Marshall et al., 2010).

Therefore, given the paucity of existing evidence, this study aimed to evaluate the association between antidepressant use in late-gestation and maternal psychiatric illness on breastfeeding rates at discharge from hospital.

Methods

Ethical Approval

This study was approved by the Women's and Children's Health Network (WCHN) Human Research Ethics Committee.

Study Design and Setting

Retrospective cohort study relating to all live births in the Women's and Children's Health Network (WCHN) between January 2001 and December 2008. The study used linkable health administrative data that included the Women's and Children's Hospital (WCH) Perinatal Statistics Collection (PSC) and the WCH Pharmacy Dispensing Records. The WCH is a specialist metropolitan tertiary level teaching hospital and South Australia's largest maternity and obstetric service, providing care for over 4000 pregnancies each year.

Study Sample

During the study period there were a total of 34,954 births. Women who were eligible for inclusion in the analysis were those who gave birth to a singleton, live born infant (n = 32,662).

Measures

Antidepressant use and psychiatric illness.

Data on exposure to antidepressants during pregnancy were obtained from the WCH Pharmacy Dispensing Records. Women were classified as exposed if they were dispensed an antidepressant during late-gestation (second and third trimesters). The hospital pharmacy dispensing records have previously been validated as an indicator of exposure to antidepressants in late pregnancy, including exposure around the time of delivery (Grzeskowiak, Gilbert, & Morrison, 2010). In an effort to obtain a suitable comparison group consisting of women with similar underlying disease as those exposed to antidepressants during pregnancy, we identified a cohort of women with an identified psychiatric illness

during pregnancy but who were not dispensed an antidepressant (disease comparison). The remaining group consisted of women who did not have a psychiatric illness and were not dispensed an antidepressant (non-exposed).

Breastfeeding status.

The primary outcome measure was breastfeeding status at discharge from hospital, which is routinely assessed and recorded on discharge for all women who deliver in the hospital. These data are collected and stored within the electronic WCH PSC.

Covariates.

The WCH PSC contains data on every live birth and late fetal death occurring at the WCH. Data are collected from each woman's medical records after delivery by a specially trained research midwife. This is undertaken using a structured coding sheet. A more detailed description of the electronic data collected can be found elsewhere (Grzeskowiak, Gilbert, & Morrison, 2012). In addition to data on breastfeeding outcomes, the PSC was used to obtain data on a range of potential confounders including maternal age, parity, smoking status, race, socioeconomic status, history of substance abuse, year of delivery, use of other psychotropic medications, and the presence of maternal psychiatric illness. Women were defined as multiparous if they had ≥ 2 deliveries, including the pregnancy in question. Socioeconomic status for each woman was determined using her residential postcode at the time of delivery, as described in previous studies (Grzeskowiak et al., 2012). Data regarding antiepileptic, antipsychotic and anxiolytic use were also included. Preterm birth was defined as < 37 weeks gestation. Of note, all supplementary birth records are checked manually for completeness and data discrepancies and then go through a series of automated validation procedures during data entry. The information in the PSC has been previously validated and has been shown to be reliable when compared with hospital case records (Pregnancy Outcome Unit, 2001).

Data Analyses

Differences between groups in relation to breastfeeding status at discharge from hospital were compared using a χ^2 test in addition to logistic regression models, generating odds ratios (ORs) and 95% confidence intervals (CIs). Adjustments were undertaken for the following potential confounders including maternal age, parity, smoking status, race, socioeconomic status, history of substance abuse, year of delivery and use of other psychotropic medications. Due to potential impact of preterm birth and neonatal hospital admission on breastfeeding at maternal discharge from hospital, additional analyses were undertaken following stratification of the cohort according to these variables. Statistical significance was defined as a 2-sided $p < 0.05$. All statistical analyses were undertaken using STATA 11 (Stata, College Station, Texas).

Results

Among the total eligible cohort (n = 32,662), 575 (1.8%) women were dispensed an antidepressant in late gestation (exposed), 1,552 (4.8%) had a reported psychiatric illness during pregnancy but were not dispensed an antidepressant (disease comparison), and 30,535 (93.5%) had no reported psychiatric illness during pregnancy and were not dispensed an antidepressant (non-exposed).

Selective Serotonin Reuptake Inhibitors (SSRIs) were the most commonly dispensed class of medications (n=431; 75%), with all women identified as using monotherapy. Types of antidepressants included; sertraline [n=200], citalopram [n=139], venlafaxine [n=68], paroxetine [n=53], amitriptyline [n=30], fluoxetine [n=21], fluvoxamine [n=18] and mirtazapine [n=12].

Compared with women in the disease comparison group, exposed women were more likely to be older, of higher parity, non-smokers, be dispensed an antipsychotic or anxiolytic and deliver by caesarean section (**Table 1**). Compared with non-exposed women, exposed

women were more likely to be older, of higher parity, smokers, Caucasian, substance users, be dispensed an antiepileptic, antipsychotic or anxiolytic and deliver by caesarean section. Preterm birth (< 37 weeks) and neonatal admission to hospital occurred more frequently in exposed women in comparison with women both in the disease comparison group and those who were non-exposed.

Women exposed to an antidepressant were significantly less likely to be breastfeeding their infants at discharge from hospital compared with non-exposed women (**Table 2**), but no statistically significant difference was observed when compared with women in the disease comparison group (**Table 3**). Women in the disease comparison group were also significantly less likely to be breastfeeding at discharge compared with non-exposed women (**Table 3**).

In stratified analyses, compared to women in the disease comparison group, women exposed to antidepressants were significantly less likely to be breastfeeding their infants at discharge from hospital if their neonate was not admitted to the neonatal unit or was delivered at term (adjusted OR 0.73; 95% CI 0.55-0.98) (**Table 3**). In contrast, no associations were observed between antidepressant use and breastfeeding among the strata whose neonates were admitted to the neonatal unit or who delivered preterm.

When examined according to type of antidepressant used, the proportion of women breastfeeding at discharge from hospital varied from 66% for paroxetine to 94% for fluvoxamine, but individual differences between antidepressants were not statistically significant (P=0.075; individual data not shown). Further sub-group analyses among women with a psychiatric illness identified a significant linear reduction in breastfeeding rates according to the number of psychotropic medications (e.g. anti-epileptics, benzodiazepines, antidepressants, antipsychotics) women were taking. For women taking 0, 1, 2, or 3 psychotropics in total, the corresponding breastfeeding rates were 82%, 79%, 66%, and 47% respectively (p_{trend} <0.001). Among women exposed to antidepressants in late gestation,

women also taking antipsychotics had significantly lower rates of breastfeeding at discharge (46%) compared with women also taking anxiolytics (72%) or antiepileptics (87%). Following the exclusion of women exposed to psychotropics other than antidepressants (N=583), when compared to non-exposed women, a similar association between antidepressant use (adjusted OR 0.60; 95% CI 0.47-0.77) and reduced breastfeeding at discharge from hospital was observed.

Discussion

When examining the association between antidepressant use and breastfeeding outcomes, these findings are consistent with those by Gorman et al. (2012) who reported antidepressant use at any stage during pregnancy was significantly associated with reduced rates of breastfeeding initiation, however Gorman et al. (2012) did not account for underlying maternal illness. In contrast, while the findings of Bogen et al. (2010) demonstrated antidepressant use in pregnancy was negatively associated with breastfeeding intention, and continued antidepressant use following delivery was negatively associated with 12-week breastfeeding status, the presence of depressive symptoms in pregnancy was not associated with breastfeeding intention, initiation or duration. The findings by Bogen et al. (2010) would suggest antidepressant use, rather than underlying maternal illness, is the key factor influencing breastfeeding outcomes.

When stratified according to mothers whose infants were not admitted to hospital or were born at term, the significant association between antidepressant use and reduced likelihood of breastfeeding at discharge from hospital among exposed mothers compared to the disease control group was unexpected. Given maternal antidepressant use is a well noted risk factor for preterm birth and neonatal withdrawal symptoms, both of which often lead to admission to the neonatal unit (Grzeskowiak, Gilbert, & Morrison, 2011), one could expect that these mothers may be less likely to breastfeed their infants through possible guilt of

exposing them to antidepressants during pregnancy. One could hypothesise that the lack of an association among the group whose infants were admitted to hospital or were preterm could relate to the increased breastfeeding supports provided to these mothers in the neonatal unit. It is possible that such supports may have been able to overcome whatever challenges antidepressants use or underlying maternal illness may pose. These mothers may also have been encouraged to breastfeed in an effort to reduce the incidence or severity of potential neonatal withdrawal from the antidepressant or other psychotropic medications. In contrast, the group of mothers whose infants did not require additional neonatal care may not have received such additional support or attention.

Antidepressants aside, the presence of maternal psychiatric illness such as depression has been previously demonstrated itself to be associated with a reduction in breastfeeding intention, initiation, and duration (Bascom & Napolitano, 2016; Hatton et al., 2005). A recent study explored specific reasons for breastfeeding discontinuation among women with postnatal depression and observed that the main factors related to maternal lactation issues rather than psychosocial or convenience issues (Bascom & Napolitano, 2016). While lactation issues, such as perceived low milk supply, can often be addressed through appropriate lactation support, it has been demonstrated that maternal illness can negatively impact milk supply. Links between maternal stress and impaired lactogenesis have been observed in human and animal models (Dewey, 2001). Such an underlying physiological effect may therefore not be so easily modifiable without addressing the underlying cause and ensuring women are receiving appropriate treatment for their psychiatric illness.

This leads to a focus on a common treatment for a range of psychiatric illnesses, antidepressants. Despite increasing evidence supporting the safety of antidepressants in lactation, maternal and clinician safety concerns may be a factor associated with reduced breastfeeding rates. Data largely demonstrate small amounts of antidepressants are

transferred into breast milk with infant plasma levels reported as undetectable or not of clinical significance (Kendall-Tackett & Hale, 2010). In general, misinformation surrounding the use of antidepressants in breastfeeding is a likely contributor to safety concerns regarding their use in this population. It is well recognised patients use Internet based resources to obtain health information, however many of these may be of poor quality and are often unreferenced or based on limited scientific evidence (Fioretti, Reiter, Betrán, & Torloni, 2015). Health professionals have a responsibility to equip women with the critical questions to assess the quality of information they are viewing and direct them to reputable internet sources (Jesper, 2015). Manufacturer's Consumer Medicines Information (CMI) is a misleading source of information for women (Amir, 2007); the statements are often cautious and in our experience negatively perceived by women. Studies have shown health professionals possess varying knowledge on the safety of medications in breastfeeding and frequently obtain information through manufacturer Product Information (de Ponti, Stewart, Amir, & Hussainy, 2015; Jayawickrama, Amir, & Pirotta, 2010). While the Product Information is readily accessible through prescribing software, information is often outdated and rarely advises a medication is safe in breastfeeding despite supporting studies. It is important the dissemination of correct information extends beyond breastfeeding women. Clinicians need to be aware of resources that are readily available to address the safety of medications in lactation, including the National Library of Medicines Drugs and Lactation Database (LactMed; http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm), textbooks (Hale & Rowe, 2014) and locally based Teratology or Medicines Information Services (Grzeskowiak, 2015). Increased awareness of these resources would assist clinicians and patients to make better informed decisions around medication use in breastfeeding.

Concern regarding maternal psychiatric illness may also influence breastfeeding rates. Poor sleep quality has been shown to worsen symptoms of psychiatric illness and as such

women may be advised against breastfeeding in order to reduce adverse impacts on mental health. We also noted multiple maternal psychotropic medication use was negatively associated with breastfeeding rates. This may be reflective of the severity of maternal illness and anxiety regarding the safety of polypharmacy in lactation.

A strength of this study is the comparison between breastfeeding initiation rates in women taking antidepressants with women having a psychiatric illness but no antidepressant use. As such, we were able to explore breastfeeding rates, taking into account unmeasured factors associated with having a psychiatric illness that we were not able to adjust for in the multivariate analysis. In comparison, other studies did not adjust for underlying maternal disease.

There are a number of limitations associated with this study. Firstly, no formal assessment for determinants of intention to breastfeed was undertaken, therefore it is possible some women did not intend to breastfeed irrespective of antidepressant use. Secondly, there was no measure of the type and severity of maternal psychiatric illness, which would have added to understanding the independent effects of psychiatric illness on breastfeeding outcomes. As such, there remains the potential for confounding due to underlying severity of psychiatric illness. Thirdly, the dose and indication of antidepressant use was not assessed. These factors may play an important role in decisions on breastfeeding. For example, women taking higher doses may be advised against breastfeeding by their clinician. Fourthly, this was a single site study at a large specialist public metropolitan tertiary level teaching hospital and thus it is not clear if these findings are generalisable to all women. Lastly, we were not able to determine if the women were still taking the medication while breastfeeding. It is possible they may have been taking it at the time of delivery but stopped soon after in order to breastfeed. Further research is warranted to determine what happens with antidepressant

use following delivery and during breastfeeding and the outcomes on maternal and infant/child health.

Conclusion

Antidepressant use is associated with a reduced likelihood of breastfeeding at discharge from hospital, but this association appears to be strongly influenced by factors such as underlying maternal psychiatric illness and perinatal outcomes including preterm birth and neonatal hospital admission. While the use of antidepressants did not appear to have an overall strong influence on breastfeeding outcomes independent of underlying maternal psychiatric illness, other aspects worthy of future research include the impact of information sources on clinician and patient decisions regarding medication safety in lactation, as well as longer-term breastfeeding outcomes in women using antidepressants in lactation. Identification of these factors would further assist in elucidating the most appropriate way to educate and support women with a psychiatric illness in order to improve breastfeeding rates. It is likely an individual approach with tailored recommendations will provide the greatest benefit to these patients. Overall, women taking antidepressants and women with a psychiatric illness may benefit from additional education and support to improve breastfeeding rates.

Conflict of Interest

None

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Table 1. Demographic and Clinical Measures for Women Exposed to Antidepressants, Psychiatric Illness Without Antidepressants, or Neither During Pregnancy

Characteristic	Antidepressant Use (n=575) n (%)†	Psychiatric Illness/No Antidepressant Use (n=1 552) n (%)†	Unexposed Control (n=30 535) n (%)†
Age (years)			
≤19	27 (4.7)	125 (8.1)	1 526 (5.0)
20-34	423 (73.6)	1 148 (74.0)	23 347 (76.5)
≥35	125 (21.7)	279 (18.0)	5 662 (18.5)
Parity≥1	375 (65.7)	877 (56.8)	16 869 (55.5)
Smoking Status			
Non-Smoker	359 (63.8)	856 (55.6.0)	23 351 (78.8)
Quit During Pregnancy	20 (3.6)	98 (6.4)	1 184 (4.0)
Smoker	184 (32.7)	574 (37.6)	5 115 (17.3)
Socioeconomic Status, SEIFA			
5 (Highest)	113 (19.7)	276 (17.8)	5 947 (19.5)
4	107 (18.6)	283 (18.3)	6 127 (20.1)
3	99 (17.3)	311 (20.1)	5 618 (18.5)
2	106 (18.5)	281 (18.1)	6 111 (20.1)
1 (Lowest)	149 (26.0)	399 (25.7)	6 650 (21.8)

Characteristic	Antidepressant Use (n=575) n (%)†	Psychiatric Illness/No Antidepressant Use (n=1 552) n (%)†	Unexposed Control (n=30 535) n (%)†
Race			
Caucasian	526 (91.5)	1 361 (87.7)	23 953 (78.4)
Asian	13 (2.3)	55 (3.5)	3 601 (11.8)
Other	36 (6.3)	136 (8.8)	2 981 (9.8)
Substance Abuse	50 (8.7)	174 (11.2)	747 (2.5)
Psychotropic Medication Use			
Antiepileptic	15 (2.6)	33 (2.1)	211 (0.7)
Antipsychotic	36 (6.3)	47 (3.0)	0
Anxiolytic	54 (9.4)	225 (14.5)	0
Delivery Type			
Caesarean Section	211 (36.7)	463 (29.8)	8 408 (27.5)
Normal Vaginal Delivery	364 (63.3)	1 089 (70.2)	22 127 (72.5)
Neonate Admitted to Hospital	236 (41.0)	404 (26.0)	5 756 (18.9)
Preterm Birth	121 (21.0)	179 (11.5)	3 233 (10.6)

Abbreviations: SEIFA, Socio-Economic Indexes for Areas

† Percentages are calculated from non-missing data

Table 2. Number of Women Breastfeeding at Discharge from Hospital According to Maternal Exposure to Antidepressants, Psychiatric Illness Without Antidepressants, or Neither During Pregnancy

	Antidepressant Use (n=575)			Psychiatric Illness/No Antidepressant Use (n=1,552)			Control (n=30,535)			
	Total	**Number Breastfeeding**	**% (95%CI)**	**Total**	**Number Breastfeeding**	**% (95%CI)**	**Total**	**Number Breastfeeding**	**% (95%CI)**	***p*-value[†]**
Entire Cohort (N=32,662)	575	445	77.4 (73.8-80.6)	1,552	1,253	80.7 (78.7-82.6)	30,535	27,130	88.9 (88.5-89.2)	<0.001
Neonate Admitted to NNU										
Yes (n=6,396)	236	175	74.2 (68.2-79.3)	404	272	67.8 (63.1-72.2)	5,756	4,812	83.6 (82.6-84.5)	<0.001
No (n=26,266)	339	270	79.6 (75.0-83,6)	1,148	979	85.3 (83.1-87.2)	24,779	22,318	90.1 (89.7-90.4)	<0.001
Preterm Birth										
Yes (n=3,533)	121	94	77.7 (69.4-84.3)	179	131	73.2 (66.2-79.2)	3,233	2,715	84.0 (82.7-85.2)	<0.001

No	454	351	77.3	1,373	1,122	81.7	27,302	24,414	89.4	<0.001
(n=29,129)			(73.3-80.9)			(79.6-83.7)			(89.1-89.8)	

Abbreviations: CI, confidence interval

† *p*-value calculated from χ^2 test

Table 3. Univariate and Multivariate Logistic Regression Models of Breastfeeding Rates at Discharge from Hospital According to Maternal Exposure to Antidepressants, Psychiatric Illness Without Antidepressants, or Neither During Pregnancy

	Antidepressant Use Vs. Control		**Antidepressant Use Vs. Psychiatric Illness/No Antidepressant Use**		**Psychiatric Illness/No Antidepressant Use Vs. Control**	
	Crude OR (95% CI)	**aOR[†] (95% CI)**	**Crude OR (95% CI)**	**aOR[†] (95% CI)**	**Crude OR (95% CI)**	**aOR[†] (95% CI)**
Entire Cohort (N=32,662)	**0.43 (0.35-0.53)**	**0.63 (0.50-0.80)**	0.82 (0.65-1.03)	0.83 (0.65-1.07)	**0.53 (0.46-0.60)**	**0.75 (0.64-0.88)**
Neonate Admitted to NNU						
Yes (n=6,396)	**0.56 (0.42-0.76)**	0.85 (0.58-1.23)	1.36(0.95-1.95)	1.28 (0.86-1.92)	**0.41 (0.33-0.52)**	**0.65 (0.49-0.86)**

No (n=26,266)	**0.43 (0.33-0.56)**	**0.58 (0.42-0.79)**	**0.68 (0.50-0.92)**	**0.70 (0.50-0.97)**	**0.64 (0.54-0.76)**	**0.82 (0.68-0.99)**
Preterm Birth						
Yes (n=3,533)	0.66 (0.43-1.03)	1.15 (0.67-1.98)	1.28 (0.74-2.19)	1.24 (0.66-2.32)	**0.52 (0.37-0.73)**	0.83 (0.54-1.30)
No (n=29,128)	**0.40 (0.32-0.50)**	**0.54 (0.41-0.71)**	**0.76 (0.59-0.99)**	**0.73 (0.55-0.98)**	**0.53 (0.46-0.61)**	**0.74 (0.62-0.87)**

Abbreviations: OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval

† OR adjusted for maternal age, parity, smoking status, race, socioeconomic status, substance abuse, year of delivery, psychotropic medication use