Use of antidepressants during pregnancy among women in Iceland 2003 – 2012:

A nationwide population-based study

Dagný Baldvinsdóttir

Ritgerð til meistaragráðu
Háskóli Íslands
Læknadeild
Námsbraut í Lýðheilsuvísindum
Heilbrigðisvísindasvið

HÁSKÓLI ÍSLANDS

Notkun þunglyndislyfja á meðgöngu meðal kvenna á Íslandi 2003 – 2012:

Lýðgrunduð rannsókn á landsvísu

Dagný Baldvinsdóttir

Ritgerð til meistaragráðu í Lýðheilsuvísindum

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Abstract

Antidepressant use during pregnancy has increased during the past decades, especially in the West. In this study, we aimed to describe the prevalence of antidepressant use during pregnancy among women in Iceland 2003 – 2012, according to maternal and pregnancy-related characteristics.

This is a nationwide population-based drug utilization study based on data from the National Medicines Registry and the Medical Birth Registry in Iceland. The study population comprised all pregnancies in Iceland that resulted in either a live birth or a stillbirth after gestational week 22 from January 1st 2003 through December 31st 2012 (N = 44775). Antidepressant exposure was defined as one or more dispensed drugs from 90 days before the last menstrual period (LMP) until delivery and accorded to the World Health Organization Anatomic Therapeutic Chemical classification system (N06A). Co-medication of anxiolytics (N05B) and hypnotics and sedatives (N05C) was assessed.

Overall, 3658 (8.2%) of 44,775 pregnancies were exposed to antidepressants during pregnancy. The youngest women (<25 years) and oldest women (>35 years) had a higher prevalence (9.1%, 9.6%) of antidepressant use than women between 25 – 35 years (7.5%), while prevalence of use increased with parity (0, 1, 2, >2) with a prevalence of 7.0%, 7.8%, 9.8% and 13.8% respectively. Antidepressant use was higher among single women than among those cohabiting (14.4% vs. 7.0%). The annual prevalence of antidepressant use varied by study year, from 7.5% to 9.5%. Selective serotonin reuptake inhibitors (SSRIs) were the most commonly used antidepressants, with 3158 (7.0%) exposed pregnancies. The prevalence of antidepressant use decreased with each passing trimester of pregnancy; from 6.1% before LMP to 4.5%, 3.6% and 2.9% in 1st, 2nd and 3rd trimesters respectively. In about one-third of exposed pregnancies, women were also dispensed anxiolytics, hypnotics or sedatives.

In line with an overall widespread use of antidepressants in Iceland, use among pregnant women was relatively high in 2003 - 2012, but varied by women's characteristics and decreased by half over the course of the pregnancy period.

Ágrip

Notkun þunglyndislyfja á meðgöngu hefur aukist á undanförnum áratugum, sérstaklega í vestrænum löndum. Markmið þessarar rannsóknar var að lýsa algengi á notkun þunglyndislyfja á meðgöngu og notkunarmynstri meðal kvenna á Íslandi á árunum 2003 - 2012.

Rannsóknin er lýsandi lyfjanotkunarrannsókn sem byggist á samkeyrslum á gögnum úr lyfjagagnagrunni Embættis landlæknis og fæðingarskrá. Þýði rannsóknarinnar voru allar meðgöngur, sem lauk með lifandi eða andvana fæðingu eftir 22. viku meðgöngu, frá 1. janúar 2003 til og með 31. desember 2012 (N = 44775). Notkun þunglyndislyfja var skilgreind sem einn eða fleiri útleystir lyfseðlar frá 90 dögum fyrir síðustu tíðir fram að fæðingu og í samræmi við lyfjaflokkunarkerfi Alþjóðaheilbrigðisstofunarinnar (sem lyfjaflokkur N06A). Samhliða lyfjameðferð með kvíðastillandi lyfjum (N05B), róandi- og svefnlyfjum (N05C) var einnig könnuð. Þunglyndislyf komu við sögu í alls 3658 (8,2%) meðgöngum af 44775 meðgöngum í rannsókninni. Notkun á þunglyndislyfjum meðal yngri kvenna (<25 ára) og eldri kvenna (>35 ára) var hærri (9.1%, 9.6%) en hjá konum 25 – 35 ára (7.5%) og algengið jókst með fjölda barna (0, 1, 2, >2) (7.0%, 7.8%, 9.8%, 13.8%). Þunglyndislyfjanotkun var algengari hjá einhleypum konum en þeim sem voru í sambúð (14.4% vs. 7.0%). Árlegt algengi þunglyndislyfjanotkunar breyttist lítillega á milli ára eða úr 7,5% í 9,5%. Sérhæfðir serótónín endurupptöku hemlar (SSRIs) voru algengasti þunglyndislyfjaflokkurinn en í alls 3158 (7,0%) meðgöngum notuðu konur SSRIs skömmu fyrir eða á meðgöngu. Algengi þunglyndislyfjanotkunar lækkaði þegar leið á meðgöngu; úr 6,1% fyrir síðustu tíðir í 4,5%, 3,6% og 2,9% á fyrsta, örðum og þriðja þriðjungi meðgöngu. Í um þriðjungi meðganga, leystu konur líka út lyfseðil fyrir kvíðastillandi lyfjum, svefnlyfjum eða róandi lyfjum.

Í samræmi við almennt víðtæka notkun þunglyndislyfja á Íslandi var notkun slíkra lyfja hlutfallslega há meðal kvenna á meðgöngu á árunum 2003 – 2012. Algengi þunglyndislyfjanotkunar var háð ýmsum lýsandi bakgrunnsþáttum kvenna og minnkaði um helming á meðan á meðgöngui stóð.

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List of Abbreviations

ASD	Autism spectrum disorder
ATC	Anatomical Therapeutic Chemical
DDD	Defined daily dose
EMA	European Medical Agency
FDA	Food and Drug Administration
LMP	Last menstrual period
MAOI	Monoamine oxidase inhibitor
NICE	National Institute of Health and Clinical Excellence
OECD	Organization for Economic Co-operation and Development
SNRI	Selective norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricliclic antidepressant
WHO	World Health Organization

Introduction

1 Depression in pregnancy

Depression is a common disease, which at least 350 million people worldwide suffer from (World Health Organization, 2015). Depression often starts at a young age, the main symptoms being persistent sadness, low energy and difficulty in functioning normally (World Health Organization, 2015). Women are more likely to be depressed than men and the rates are higher during childbearing years than at other times of life (World Health Organization, 2015). Depression during pregnancy is common and is reported to affect 7% - 25% pregnancies (Bakker, Kölling, Van Den Berg, De Walle, & De Jong van den Berg, 2007; Cohen et al., 2006) with the highest prevalence in the low-income countries (Lovisi, Lopez, Coutinho, & Patel, 2005; Rahman, Iqbal, & Harrington, 2003). There are several potential reasons for a higher probability of depression during this major physiological process and life event than during other phases of life (O'Keane & Marsh, 2007).

The main risk factor for depression during pregnancy is women's previous history of depression, but other risk factors are maltreatment in childhood, single or adolescent mothers, unplanned pregnancy, low income, having more than three children, poor social support and domestic violence (Dietz et al., 2007; National Institute for Health and Clinical Excellence, 2014; Shaw, Lawlor, & Najman, 2006; Yonkers et al., 2009). As the main factor for depression during pregnancy is history of depression, one of the reasons might be discontinuation of antidepressants during pregnancy. A study of women who suffered from major depression before pregnancy showed that women who discontinued antidepressant treatment before or close to conception were more likely to have a relapse during pregnancy than those who maintained antidepressant treatment (Cohen et al., 2006). Poorer birth outcomes are often linked to depression. Another co-factor for depression and poorer birth outcomes is the unhealthy lifestyle that is often associated with depression, including smoking, alcohol and abuse of harmful substances, poor attendance to prenatal care, and risk of self-harm or suicide." (Dietz et al., 2007; Yonkers et al., 2009).

Depression during pregnancy is associated with various adverse pregnancy outcomes, including increased risks of preterm delivery (Hoffman & Hatch, 2000; Orr, James, & Blackmore Prince, 2002), interventions during delivery (Bonari et al., 2004; Talati et al., 2007; Weissman et al., 2006), low birth weight (Hoffman & Hatch, 2000; Orr et al., 2002), and postpartum depression (Beck, Records, & Rice, 2006; Bonari et al., 2004; Talati et al., 2007; Weissman et al., 2006).

Depression during pregnancy also increases the likelihood of postpartum depression, with consequences such as difficulties with the mother and child connection, the care of the infant, the relationship with the partner, and the care of other children in the home (National Institute for Health and Clinical Excellence, 2014).

In prenatal care it is recommended to ask questions about women's history of depression and to screen questions for depression (American College of Obstetricians and Gynecologists, 2010; Stewart, 2011). The National Institute for Health and Clinical Excellence (NICE) recommend three screening questions for depression during pregnancy (Table 1) (National Institute for Health and Clinical Excellence, 2014). The Directorate of Health in Iceland recommends asking pregnant women the same questions from NICE in their guidelines for antenatal care (Directorate of Health Iceland, 2010) .

Table 1 Screening Questions* for Depression during Pregnancy

During the past month, have you been bothered by feeling down, depressed, or hopeless?
During the past month, have you been bothered by having little interest or pleasure in doing things?
If the answer to either question is "yes," ask "Is this something you feel you need or want help with?"

* Questions are from the National Institute for Health and Clinical Excellence (National Institute for Health and Clinical Excellence, 2014).

1.1 Antidepressants and indications

Antidepressants are one of the most common treatment options for depression, together with psychotherapy such as cognitive behavioural therapy, interpersonal therapy and family-focused therapy (National Institute of Mental Health, 2016). Antidepressants were introduced to the market in the late 1950s. Their use was not very common at first due to a poor side-effect profile. The older classes of antidepressants included tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) (Anderson, 2000; Williams et al., 2000). The newer classes of antidepressants – selective serotonin reuptake inhibitors (SSRIs) that were first introduced to the market in the 1980s and selective norepinephrine reuptake inhibitors (SNRIs) that appeared in 1994 – are regarded as a better choice than the older antidepressants because they do not cause as many side effects, are less likely to be harmful if taken in overdose, and seem to help in a larger group of depressive and anxiety disorders (Diav-Citrin & Ornoy, 2012; National Institute of Mental Health, 2016). The way SSRIs and SNRIs seem to work is by inhibiting the reuptake of serotonin and norepinephrine in brain regions that are involved in mood regulation (Koren & Nordeng, 2012).

In addition to depression, antidepressants are used in treatment of heath conditions like anxiety, chronic pain, insomnia, nocturnal enuresis, eating disorders and Tourette syndrome. Treatment with antidepressants during pregnancy, especially with SSRIs, has increased during the past decade although research on their use in pregnancy is still somewhat limited (National Institute of Mental Health, 2016).

1.1.1 Antidepressant use during pregnancy – use and trends in Western countries

Antidepressant use in pregnancy has been increasing over the past decade, both in Europe and in the United States (Alwan, Reefhuis, Rasmussen, Olney, & Friedman, 2007; Bakker et al., 2007; Kieler et al., 2012; Petersen, Gilbert, Evans, Man, & Nazareth, 2011). The far most used antidepressants during pregnancy are SSRIs (Alwan et al., 2007; Bakker et al., 2007; Kieler et al., 2012; Petersen et al., 2011). A Danish study based on a nation-wide cohort of 912,322 pregnancies showed that from 1997 to 2010 the prevalence of antidepressant use among pregnant women in Denmark increased from 0.2% to 3.2% (Jimenez-Solem et al., 2013). In this study, SSRI use accounted for 88.7% of

antidepressant use (Jimenez-Solem et al., 2013). In a very recent Nordic study based on data from 2008 - 2012, the prevalence of SSRI and SNRI use during pregnancy varied by country, ranging from 1.8% in Norway, 3.7% in Sweden and Denmark and 7.0% in Iceland (Zoega et al., 2015). In a study from the Netherlands, based on data from a population-based prescription database, the prevalence of SSRI use in pregnancy was shown to double between 1995 and 2004 (Bakker et al., 2007). Similarly, in the United Kingdom a similar trend is observed. In a study conducted from The Health Improvement Network primary care database, prescription of antidepressants in pregnancy was found to quadruple from 1992 to 2006 (Petersen et al., 2011). In a retrospective study that was conducted using databases from 7 health plans in the United States, the prevalence of SSRI use during pregnancy increased from 1.5% in 1996 to 6.2% in 2005 (Andrade et al., 2008). Huybrechts et al. (2013) identified pregnant women aged 12 – 55 who were enrolled in Medicaid (public insurance) and found that 8.1% of women took an antidepressant at some point during pregnancy between 2000 and 2007. The higher use of antidepressants among pregnant women in the United States compared with Europe may be explained by a generally more widespread use of antidepressants among the total population in the United States than elsewhere.

Although most studies on antidepressant use during pregnancy demonstrate increased use over the last decades, many women with depression seem to discontinue to take antidepressants once they find out they are pregnant. In a study from the Netherlands, almost 60% of the women who used antidepressants before pregnancy stopped taking them in the first trimester (Ververs et al., 2006). Utilization studies on prevalence of antidepressant use during pregnancy show that the use decreases with each trimester that passes (Huybrechts et al., 2013; Jimenez-Solem et al., 2013; Zoega et al., 2015). The same trend is seen in this study.

Not many studies have been published about antidepressant use during pregnancy and co-medication of anxiolytics and/or hypnotics, but in the Nordic study from Zoega et al. (2015) the concurrent use of anxiolytics and/or hypnotics with antidepressant use during pregnancy was observed. The use of anxiolytics and hypnotics during pregnancy has been researched in some other studies but not as co-medication with antidepressants (Margulis et al., 2013).

Only a few studies have been conducted on a countrywide basis about the utilization patterns of antidepressants in pregnancy in terms of the patient and treatment characteristics. The Danish study mentioned above was based on nationwide data and the aim of the study was the prevalence of antidepressant use during pregnancy in Denmark from 1997 – 2010 (Jimenez-Solem et al., 2013), while the Nordic study about the use of SSRIs and SNRIs during pregnancy was based on nationwide data from Denmark, Iceland, Norway and Sweden (Zoega et al., 2015). Some studies are based on information from self-reported surveys, insurance or reimbursement data. However, these data sources are often limited to specific social or regional groups or, in the case of self-reports, the memory of individuals can be unreliable which may hinder solid conclusions (Bennett, Marcus, Palmer, & Coyne, 2010; Kornum, Nielsen, Pedersen, Mortensen, & Norgaard, 2010).

1.1.2 Antidepressant use during pregnancy and potential adverse risks for mother and infant

Antidepressants are used to treat depression during pregnancy though their efficacy in pregnancy has not been proven. Although SSRIs have been shown to work well in treating depression, safety profiles and specific indications for use in pregnancy are still lacking (Alwan et al., 2007; Kieler et al., 2012). Many studies have been published about the risk of congenital malformations in association with antidepressant use, mainly of SSRIs, during pregnancy: some of these report no increased risk of congenital malformations for the infant (Margulis et al., 2013; Vasilakis-Scaramozza, Aschengrau, Cabral, & Jick, 2013), while others have reported an increased risk for several malformations, primarily an increased risk in congenital heart defects in association with antidepressant groups and specific drug types (Alwan et al., 2007; Berard et al., 2007; Diav-Citrin et al., 2008; Kallen & Otterblad Olausson, 2007; Louik, Lin, Werler, Hernandez-Diaz, & Mitchell, 2007; Oberlander et al., 2008; Pedersen, Henriksen, Vestergaard, Olsen, & Bech, 2009; Wogelius et al., 2006). All of the studies that report increased risk of congenital malformations indicate that the risk is relatively low. A few studies have highlighted increased risk in congenital malformations with the intake of paroxetine (Berard et al., 2007; Kallen & Otterblad Olausson, 2007; Reis & Kallen, 2010) while others report a connection for other SSRIs (Diav-Citrin et al., 2008; Kallen & Otterblad Olausson, 2007; Pedersen et al., 2009) and one study reports a link between congenital malformations and the use of TCAs (Reis & Kallen, 2010). However, sometimes it is unclear if the association of congenital malformations is because of the drug use or because of the underlying disease (Reis & Kallen, 2010).

On the other hand, three recent studies on the risk of persistent pulmonary hypertension (Huybrechts et al., 2015) and on birth defects (Furu et al., 2015; Huybrechts et al., 2014) indicated that the risk may be less than other studies have shown. Huybrechts et al. (2015) conducted a cohort study from 2000 to 2010 with 3,789,330 pregnant women enrolled in Medicaid in the United States, and found out that there is a potential increased risk of persistent pulmonary hypertension with maternal use of SSRIs in late pregnancy but the risk is low and lower than previous published. Huybrechts et al. (2014) conducted another study from 2000 – 2007 that included 94,9504 pregnant women who were enrolled in Medicaid in the United States. After adjusting for potential confounders, the results of this study indicated no substantial increase in the risk of cardiac malformations attributable to antidepressant use during the first trimester. Furu et al. (2015) conducted a large Nordic cohort study with databases from all five Nordic countries (Sweden, Norway, Denmark, Finland and Iceland) and found no significant increase in the prevalence of cardiac birth defects among infants exposed to SSRIs or venlafaxine *in utero*. Even though there was an increase in the prevalence of septal defects and right ventricular outflow tract defects in exposed infants, this was not significant when controlling for confounding by a sibling-controlled design. According to these studies, the risk of persistent pulmonary hypertension and birth defects is small, but less is known about the long-term outcome on children when the mother is taking antidepressants during pregnancy. A few studies have been conducted to find if the use of antidepressants during pregnancy, especially SSRIs, increases the risk of autism spectrum disorders (ASD) during childhood. According to a systematic review and meta-analysis that looked into the studies that have been conducted in this field, there might be an increase in ASD in children when

their mothers have taken SSRIs during pregnancy, though causality remains to be confirmed (Man et al., 2015). In a new study published in 2016, increased risk of ASD is seen in women who used antidepressants, specifically SSRIs, during the second and/or third trimester of pregnancy. Further research is needed to find out the association between ADS and antidepressant types and dosage during pregnancy (Boukhris, Sheehy, Mottron, & Bérard, 2016).

Although the newest studies state that the risk is low, the European Medical Agency (EMA) and Food and Drug Administration (FDA) in the United States have issued a warning, based on the latest evidence concerning the use of SSRIs during late pregnancy and increased risk of persistent pulmonary hypertension in the neonate. These bodies have also warned against exposure to paroxetine and fluoxetine during the first trimester due to an increased risk of congenital malformations, especially cardiac defects. In newly published guidelines for GPs in Iceland, SSRIs are recommended when it is necessary to treat depression during pregnancy with medication, but the use of paroxetine is not recommended (Centre of Development Iceland, 2015).

1.1.3 Antidepressant use in Iceland

In Iceland high utilization rates of psychotropic drug use have been reported among the general population (Directorate of Health Iceland, 2014) as well as among children (Zoega et al., 2009) and the elderly (Samuelsson, Zoega, Gudmundsson, & Halldorsson, 2009). In 2006 one-third of all dispensed drugs in Iceland were for people 70 years or older, and quarter of the drugs dispensed to elderly people were psychotropic (Samuelsson et al., 2009). When the Icelandic data for people from 70 – 74 years old is compared with that of Danes of the same age, the prescription of psychotropic drugs is shown to be more frequent in Iceland (Samuelsson et al., 2009). High utilization rates of psychotropic drug use are also seen among children in Iceland (Zoega et al., 2009). In 2007 the overall prevalence of psychotropic drug use was 48.7 per 1000 Icelandic children, and the most used psychotropic drug groups were stimulants and antidepressants (Zoega et al., 2009). If compared to reports from other European countries, the utilization rates of psychotropic drug use among children in Iceland in the years 2003 – 2007 is high (Zoega et al., 2009). Antidepressant use in Iceland is high and higher than in the countries around us (Directorate of Health Iceland, 2014). In a study from 2009 it is reported that antidepressant sales figures rose from 8 defined daily doses (DDD)/1000 in 1975 to 95 DDD/1000 in 2005 (Sigurdsson, Olafsdottir, & Gottfredsson, 2009). In a report from The Organization for Economic Co-operation and Development (OECD) countries from 2015, Iceland is reported to have the highest use of antidepressants per capita of all OECD countries in 2013, or 118 daily doses per 1000 people per day (OECD, 2015). It is not clear why antidepressant use is so high in Iceland, but one explanation might be the lack of other treatment options, as psychological treatment in Iceland is not reimbursed as medication. We do not know the prevalence of depression in Iceland, but in the other Nordic countries the prevalence is about 15%. If the prevalence is similar in Iceland and we compare it with the usage of antidepressants in Iceland in 2013 – which was 12% – the usage of antidepressant is maybe not that high except perhaps for children (Directorate of Health Iceland, 2014). Prescriptions for antidepressants in Iceland are fulfilled for a maximum of three months.

1.2 Pharmacoepidemiology

As the name suggests, pharmacoepidemiology is built on the fields of clinical pharmacology and epidemiology. The main purpose of pharmacoepidemiology is to study the use and effects of drugs in a large number of people (Storm & Kimmel, 2008). Pharmacoepidemiology is a relatively new field that is bridging between clinical pharmacology and epidemiology. This is done by using the techniques of chronic disease epidemiology to study the effect and use of drugs (Storm & Kimmel, 2008). Pharmacoepidemiology can be used in pre- and post-marketing research, but has primarily been used in the context of post-marketing drug surveillance where the interest for these studies has been expanding significantly. Pre-marketing studies that are conducted in the approval process of a drug cannot, before marketing, detect adverse effects that are uncommon, delayed, unique to high-risk populations, or due to misuse of the drugs by either prescribers or patients (Storm & Kimmel, 2008). Post-marketing studies can study the actual use and effects of drugs over a limited time in a large number of people. Pharmacoepidemiology is important and can contribute information about drug safety and effectiveness that is not available from premarketing studies (Storm & Kimmel, 2008)

1.2.1 Drug utilization studies

Drug utilization studies are a necessary part of pharmacoepidemiology as they describe the degree, nature and determinants of drug exposure. The World Health Organization (WHO) defines drug utilization research as “the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences“. Drug utilization studies can be divided into two study types: descriptive and analytical studies. The descriptive studies focus on the description of the drug utilization patterns and identify problem regions that need further investigation (WHO International Working Group for Drug Statistics Methodology, WHO Collaborating Centre for Drug Statistics Methodology, & Who Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services, 2003). The ultimate goal of analytical studies is to find out if a drug therapy is rational or not, by linking together drug utilization data with data on morbidity, the outcome of treatment and quality of care (WHO International Working Group for Drug Statistics Methodology et al., 2003). This study is describing the use of antidepressant drugs among pregnant women in Iceland.

1.2.2 Bias in registry- based drug utilization studies

There is a risk of bias in all pharmacoepidemiological studies and researchers need to have this in mind in the designing stage to minimize them. Nationwide registry-based studies greatly reduce the occurrence of selection bias but other forms of bias are possible (Storm & Kimmel, 2008). Firstly there is the possibility of misclassifying drug exposure: in registry-based studies we have accurate data on dispensed drugs but no information about actual drug intake. The second and probably most important confounding factor is confounding by indication, because there is always a reason for a prescription and the reason is often associated with the outcome of interest (Storm & Kimmel, 2008). When using prescription data to measure exposure, no information is available about accurate indication of use. This fact makes the risk of this kind of confounding more likely. As this study is based on prescription data, we have no information about the indication for the prescription and we cannot be sure that the antidepressants that are dispensed in this study are prescribed for the indication “depression”. Antidepressants have more indications than just depression, although depression is the most common one.

1.2.3 Drug classification system ATC/DDD

The classification system used in this study accords to the World Health Organization Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) classification (WHO Collaborating Centre for Drug Statistics Methodology, 2014). The ATC/DDD system purpose is to serve as a tool for utilization research in order to improve the quality of drug use. One aspect of this is the presentation and comparison of drug consumption statistics on a national and international level. The active substances are divided into different groups according to the organ or system on which they function, and are then further divided according to therapeutic, pharmacological and chemical features. The drug groups are classified into five levels. In the first level the drugs are divided into 14 groups that are further divided into pharmacological/therapeutic subgroups (second level). Then we have third and fourth levels that are chemical/pharmacological/therapeutic subgroups, and a fifth level that is the chemical substance subgroup (WHO Collaborating Centre for Drug Statistics Methodology, 2014).

The drugs we will study all belong to the ATC group N, which stands for Nervous system. We will primarily focus on the subgroup N06A (antidepressants). The subgroups for N06A are the following: Selective serotonin reuptake inhibitors (SSRIs), Selective norepinephrine reuptake Inhibitors (SNRIs), Non-selective monoamine reuptake inhibitors (also known as tricyclic antidepressants, TCA) and other antidepressants. The antidepressant groups used in this study are denoted by the codes shown in Table 2.

Table 2 ATC codes

N Anatomical group	Nervous system
N06 Therapeutic group	Psychoanaleptics
N06A Antidepressants	Used for depression and other related syndromes
N06AB	Selective serotonin reuptake inhibitors (SSRIs)
N06AX	Selective norepinephrine reuptake Inhibitors (SNRIs)
N06AA	Non-selective monoamine reuptake inhibitors (also known as Tricyclic Antidepressants, TCA)
N06AG, N06AX	Other antidepressants

In our study, antidepressants refers to the drugs that are shown in Table 3, which are the drugs that were used in our study and are shown here together with DDD and the date of marketing authorization in Iceland.

Table 3 Categorization of Antidepressants in the study with Defined Daily Doses (DDDs) for each

Drug	ATC Class	DDD (mg)	Date of marketing authorization
Any antidepressant	**N06**		
SSRIs	**N06AB**		
Citalopram	N06AB04	20 mg	1.4.1993
Escitalopram	N06AB10	10 mg	1.8.2002
Fluoxetine	N06AB03	20 mg	1.6.1998
Paroxetine	N06AB05	20 mg	1.4.1993
Sertraline	N06AB06	50 mg	1.10.1995
SNRIs	**N06AX**		
Venlafaxine	N06AX16	0.1 g	1.10.1998
Duloxetine	N06AX21	60 mg	1.10.1998
TCAs	**N06AA**		
Clomipramine	N06AA04	0.1 g	1.3.1977
Trimipramine	N06AA06	0.15 g	1.10.1995
Amitriptyline	N06AA09	75 mg	1.12.1972
Nortriptyline	N06AA10	30 mg / 75 mg	1.1.1985
Doxepin	N06AA12	0.1 g	1.12.1972
Other antidepressants			
Moclobemide	N06AG02	0.3 g	1.10.1990
Mianserin	N06AX03	0.15 g	1.1.1994
Mirtazapine	N06AX11	30 mg	1.12003
Bupropionum	N06AX12	0.3 g	1.9.2000
Reboxetine	N06AX18	8 mg	1.6.2000

ATC = Anatomical Therapeutic Chemical
DDD = Defined daily dose
SSRIs = Selective serotonin reuptake inhibitors
SNRIs = Selective norepinephrine reuptake inhibitors
TCAs = Tricyclic antidepressants

1.2.4 Prescription registers

There is a long history of collecting epidemiological data about death and diseases in the Nordic countries. These registers have covered the whole population and have been of high quality. Examples of epidemiological registers are the National Cancer Register, Medical Birth Register, Causes of Death Register and others (Rosen, 2002). Since the 1970s, the Nordic countries have been able to collect data on wholesale drug distribution; this data can be used to see nationwide time trends in drug utilization. But to be able to have more accurate data about accurate drug utilization in a population and to be able to link the data from other health databases it is necessary to narrow the data down to each individual. After pharmacies became electronic it was possible to collect data on

national prescriptions that contained data on all drugs dispensed in pharmacies to individuals receiving ambulatory care. These databases have been available in Finland and Denmark since 1994, from 2004 in Norway, 2005 in Sweden and from 2003 in Iceland (Furu et al., 2010; Zoega et al., 2009). The register contains information about the patient and the prescriber (age, gender, personal identifier, place of residence, physician speciality and clinic), the drug prescribed (the Nordic article number, number of packages, ATC code, DDD, prescription category, reimbursement code, prescribing date, dispensing date and price) and pharmacy data (Furu et al., 2010). The Nordic prescription register contains a lot of information but does not contain any information on indications for drug prescribing. This Nordic registers contain data on all 25 million inhabitants and give researchers in the Nordic countries an advantage over researchers from other countries, most of which do not have access to national databases like the Nordic ones (Furu et al., 2010; Rosen, 2002).

Many studies have been conducted by using the Nordic databases. For instance, it is possible to link data from the prescription register to other health databases/registers by using the unique personal identification number (PIN) that is issued to every person at birth or upon immigration (Rosen, 2002). Pharmacies are mandated by law to send in electronic data to the registers, therefore the completeness and exactness of the pharmacy records sent to the Nordic databases is high (Furu et al., 2010).

1.2.5 The Icelandic Medicines Registry

The **Icelandic Medicines Registry** contains data on all (outpatient) prescriptions dispensed from Icelandic pharmacies since January 1st 2003. It holds information at the individual level, both on patients and prescribing physicians, which is stored under encrypted personal identification numbers. The Registry records information about dates of prescribing and dispensing; the dispensing pharmacy; and data on the dispensed drug substance (brand name, formulation, package, dosage, volume, ATC codes and cost of the drug). The Registry does not hold information on the underlying indication for the drug treatment (Directorate of Health, 2015).

The Icelandic Medicines Registry was established through an Act that came into effect June 1st 2005. This provision can be found in the Medicinal Products Act no. 93/1994, together with some later amendments, and Act no. 41/2007 about the Directorate of Health and Public Health. The purpose of the Medicines Registry was to enable the Directorate of Health to fulfil its duties, i.e. to encourage the rational use of drugs and to monitor physicians' prescriptions. In the beginning the Registry could only hold person-identifiable information for a period of three years, by law, but in 2008 the time was extended to 30 years for research purpose (Directorate of Health, 2015). Today the Medicine Registry contains all data on all prescriptions dispensed from Icelandic pharmacies and nursing homes, though not from the hospitals. The accuracy of the database is high, both because the data is mostly electronic and the pharmacies are required by law to supply all information on dispensed medication via personal information encrypted to the Icelandic health insurance. (Medicinal Product Act no. 93/1994, 1994)

1.2.6 The Icelandic Birth Registry

The **Icelandic Birth Registry** contains data on all births in Iceland since 1972 and has been electronic since 1981. The Birth Registry contains data concerning pregnancy, births, issues during delivery and born infants, including place of delivery and time, parity, gestational length, treatment during delivery, residence, marital status, citizenship and date of last menstrual period [LMP] (Directorate of Health Iceland, 2010).

The main purpose of the Registry is to collect statistics and compare them with data from other countries, and also to use the data for research purposes. The other Nordic countries have similar registers and there is cooperation between them.

2 Specific aims

In the present study, we seek to answer how common the use of antidepressants is during pregnancy in Iceland. More specifically, we intend to determine the annual prevalence of antidepressant use (N06A) among pregnant women in Iceland from 2003 to 2012 and describe the patterns of utilization with respect to women's age, residency, occupation, marital status, citizenship, parity and type of antidepressant, as well as to examine co-medication of anxiolytics (N05B) and/or hypnotics or sedatives (N05C) and treatment initiation in 2nd and 3rd trimester. Further, we examine whether antidepressant utilization patterns have changed over calendar time.

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Use of Antidepressants during Pregnancy among Icelandic Women in 2003 – 2012: A Nationwide Population-Based Study

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Key Points

- The use of antidepressants during pregnancy is relatively high in Iceland compared to neighboring countries.
- Prevalence of antidepressant use during pregnancy was increased among single women, the youngest and oldest age groups and by women's parity.
- The use of antidepressants during pregnancy decreased with each trimester and treatment initiation from 2nd trimester and onwards is rare in Iceland.
- Although use of drugs with known teratogenic effects (paroxetine) has decreased over time they were still being used by little under 1% of the pregnant population in 2012.

Abstract:

Background: The legitimacy of using antidepressants as treatment for maternal depression during pregnancy remains an open debate. We aimed to describe the prevalence of antidepressant use patterns during pregnancy among women in Iceland 2003–2012 according to maternal- and pregnancy related characteristics.

Methods: A nationwide population-based drug utilization study, based on data from the National Medicines Registry and Medical Birth Register in Iceland. The study population comprised all pregnancies in Iceland, resulting in a live birth or stillbirth after gestational week 22 from January 1st 2003 through December 31st 2012 (N=44775). Antidepressant exposure was defined as one or more antidepressant drug dispensings from 90 days before last menstrual period (LMP) until delivery. Co-medication use of anxiolytics and hypnotics was also assessed.

Result: Overall 3658 (8.2%) of 44775 pregnancies were exposed to antidepressants during pregnancy of which 3158 (7.0%) were exposed to selective serotonin reuptake inhibitors (SSRIs). Prevalence of use was increased among single women, the youngest and oldest age groups and by women's parity. The annual total prevalence varied slightly by study year; between 7.5% and 9.5%, with a marked decrease in prevalence of paroxetine use (2.0% in 2003, 0.8% in 2012). Prevalence of use decreased with each trimester of pregnancy; from 6.1% before LMP to 4.5%, 3.6% and 2.9% respectively in 1st, 2nd and 3rd trimester, with new users in 2nd or 3rd trimesters representing less than 1%. In about one third of exposed pregnancies, women were also dispensed anxiolytics, hypnotics or sedatives.

Conclusions: In line with an overall widespread use of antidepressants in Iceland, use among pregnant women was relatively high in 2003-20012, but varied by women's characteristics and decreased by half throughout the pregnancy period.

Key Words – antidepressants, selective serotonin reuptake inhibitors, pregnancy.

Introduction

Depression is common among women of childbearing age[1] and during pregnancy it is estimated to have prevalence of 7-15% in economically developed countries.[1, 2] Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used class of antidepressants during pregnancy[3] and most studied with respect to utilization patterns and potential adverse risks associated with in-utero exposure.[4] Less studied are utilization patterns of selective norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and other antidepressants during pregnancy.[5, 6] The main risk factor for depression during pregnancy is a history of depression,[7] but other factors can trigger depression during pregnancy such as poor social support,[7-9] an unplanned pregnancy,[7-9] being a single or adolescent mother[7-9] and having more than three children and domestic violence.[8]

In Iceland the overall utilization of antidepressants is high; in 2013 the country was reported to have the highest use per capita of all countries within the Organisation for Economic Co-operation and Development (OECD), or 118 daily doses per 1000 inhabitants per day.[10] Very recently a study based on nationwide data from four of the five Nordic countries, demonstrated that the prevalence of SSRI and SNRI use during pregnancy was by far the highest in Iceland (7.0%), followed by Sweden and Denmark (3.7%), and Norway (1.8%).[11] A recent study from Denmark, found that in 1997-2010 the prevalence of antidepressants use among pregnant women in Denmark increased from 0.3% to 2.4%.[12] Similar increases in use have also been reported in the Netherlands and United Kingdom.[13, 14] Andrade et al.[15] demonstrated that between 1996 and 2005 the prevalence of SSRI use during pregnancy increased from 1.5% to 6.2% among women from seven health plans in the United States. In another study from the United States, based on women aged 12-55 who were enrolled in Medicaid (public insurance) during 2000-2007, 8.1% of women took an antidepressant at some point during pregnancy.[6] Many studies from Europe e.g. the Nordics, Netherlands and North America reflect an increasing use of antidepressants among pregnant women over the

past decades.[12, 13, 15-17] In general studies point towards a higher prevalence of antidepressant use among pregnant women in the United States than in Europe.

In the light of reports of high use of antidepressants among the Icelandic population, [18] we aimed to scrutinize further utilization of these drugs among pregnant women over the past decade. In-utero exposure to antidepressants may have consequences for the unborn infant although recent studies,[5,19, 20] demonstrate a lower risks of birth defects and persistent pulmonary hypertension with SSRI exposure, than previous data did.[3, 17, 21, 22] Less is still known about potential long-term effects of antidepressant exposure in-utero on child development.[23, 24] If left untreated, depression itself may also adversely affect both the mother and unborn child, with increased risks of preterm delivery,[25, 26] interventions during delivery,[27-29] low birth weight[25, 26] and postpartum depression.[27-30] Thus optimal treatment of depression during pregnancy remains a clinical challenge.

Leveraging nationwide registry data on all dispensed prescription drugs in Iceland, we sought to describe the use of antidepressants, including SSRIs, SNRIs, TCAs and a few others among pregnant women in Iceland between 2003 and 2012 with respect to maternal demographic and pregnancy related characteristics. Our main focus was to study potential trends in prevalence of use and by pregnancy trimester for the separate antidepressant substances, as well as co-medication with anxiolytics, hypnotics and sedatives and changes in prevalence of use across secular time.

Materials and Methods

Study Setting and Population

This was a nationwide population-based drug utilization study describing use of antidepressant drugs among pregnant women in Iceland. Data were obtained from the National Medicines Registry and Medical Birth Register. Linkage between these registers was performed via encrypted personal identification number, a unique number assigned to each resident at birth or immigration. The study population consisted of all women who gave

birth or experienced intrauterine death/stillbirth in Iceland after gestational week 22, from January 1st 2003 through December 31st 2012 (N= 44775).

From the Icelandic Medical Birth Register we obtained information about pregnancy dates, maternal socio-demographic- (age at delivery, residence, marital status, citizenship, place of delivery) and pregnancy characteristics (parity, date of last menstrual period [LMP], gestational length, month and year of delivery). From the National Medicines Registry, established in 2003, we obtained information about dispensed drugs in outpatient care; including dates of drug dispensing and information on the drug substance (brand name, formulation, package, dosage and volume). The Medicines Register included information on both reimbursed and non-reimbursed drugs but does not contain information on indication for drug prescribing. In Iceland a filled antidepressant prescription generally lasts for 3 months, at the maximum.

Study Drugs and Pregnancy Periods

The study drugs were classified according to the World Health Organization Anatomical Therapeutic Chemical ATC classification,[31] as substances within ATC-code N06A, including SSRIs, SNRIs, TCAs and other antidepressants (S1 Table).

Prevalence of antidepressant use during pregnancy was defined as the number of pregnant women per 100 pregnancies (%) in the population, who dispensed at least one antidepressant anytime from 90 days before the first day of last menstrual period (LMP) until delivery or end of pregnancy. We further described antidepressant use by trimester of pregnancy as a drug dispensed the following time windows: before pregnancy (T0; up to 90 days before LMP), first trimester (0 to 97 days of gestation), second trimester (98 to 202 days of gestation) and third trimester (203 days of gestation to delivery). When calculating prevalence of use during the third trimester, pregnancies ending before the end of the second trimester were not included in the denominator. Gestational length was based on the first day of LMP as estimated by prenatal ultrasound. In light of previous public health

advisories regarding use of paroxetine in early pregnancy,[32, 33] we paid special attention to the prevalence of this SSRI substance.

To assess new (incidence) use of antidepressant during pregnancy, we calculated the number of pregnant women per 100 pregnancies (%) in the population, who were dispensed an antidepressant only during the second or third trimester of pregnancy and not before LMP or during the first trimester of pregnancy.

Among all pregnancies exposed to antidepressants, we assessed co-medication of anxiolytics (ATC-code N05B), hypnotics and sedatives (ATC-code N05C) by calculating the percentage of pregnancies in which a woman had, at anytime during pregnancy (from 90 days before LMP until delivery or end of pregnancy), also dispensed a substance classified in the abovementioned groups.

Data Analysis

Using frequencies and proportions, as defined above, we described the prevalence of antidepressant use in pregnancy by drug group (any antidepressant, SSRI, SNRI, TCA, other antidepressants) and specific substances (Table 1), maternal age (≤19, 20-24, 25-29, 30 -34, 35-39, ≥ 40 years), maternal relationship status (cohabiting with other parent, not cohabitating), maternal citizenship (Icelandic, non-Icelandic), parity (0, 1, 2, >2), place of delivery (Capital, South, Southwest, North, East and West regions of Iceland),[34] month and year of delivery.

The study population was women who gave birth or experienced intrauterine death/stillbirth from January 1st 2003 through December 31st 2012. However, as data from the National Medicines Registry were not available until January 1st 2003, information on antidepressant use from 90 days before LMP through delivery was incomplete for pregnancies ending during the first 9 months of 2003.

We used R version 3.2.3. for all data description and analyses. The study was approved by the Icelandic Bioethics Committee (VSNb2008100028/03.7) and The Data Protection Authority in Iceland (2009010039ÞS/--)

Results

During the entire period of observation, 3658 (8.2%) of 44775 pregnancies were exposed to antidepressants at some point during the pregnancy period. The median age of antidepressant users was 29.1 years at the time of delivery. Antidepressant use was higher among single women than among those cohabitating (14.4% vs. 7.0%); more commonly used among women of Icelandic citizenship than non-Icelandic (8.8% vs. 2.4%). The prevalence of use increased with parity (0, 1, 2,>2) (7.0%, 7.8%, 9.8%, 13.8%) and the youngest women (<25) and oldest women (>35) had a higher prevalence (9.15%, 9.6%) of antidepressant use than women between 25 – 35 years (7.55%). When the data were stratified by age and parity simultaneously, prevalence of use was highest among the youngest (<19 years) nulliparous women (11.0%) and the oldest (≥40 years) multiparous women (13%).

Over the 10-year study period the prevalence of antidepressant use in pregnancy varied between 7.5 and 9.5 per 100 pregnancies, following a u-shaped pattern (Figure 1). SSRIs were by far the most commonly used antidepressants in the study population throughout the study period, with an overall prevalence of 7.0 per 100 pregnancies (Figure 1). Each of the other antidepressant groups had a use prevalence of less than 1 per 100 pregnancies. Of the separate substances, sertraline was most commonly used drug, in 3.2 per 100 pregnancies, followed by fluoxetine (1.9 per 100), escitalopram (1.3 per 100) and paroxetine (1.0 per 100) (Table 2). The prevalence of paroxetine decreased by calendar year from 2% in 2003 to 0.8% in 2012 (Figure 1).

Antidepressant use was most prevalent in the period before LMP (6.1%) and decreased with each passing trimester of pregnancy, with a total of 4.5%, 3.6% and 2.9% of pregnancies exposed in 1st, 2nd and 3rd trimester, respectively (Table 2, Figure 2). The incidence of pregnant women that were only dispensed an antidepressant during the second and third trimester of pregnancy, i.e. not before the end of first trimester, was 0.8 per 100 pregnancies.

Co-medication of anxiolytics, hypnotics or sedatives with antidepressant use was prevalent in 1106 (30.2%) pregnancies. As demonstrated in S2 Table, co-medication with any of these drugs was most prevalent in pregnancies exposed to TCAs (31.1%).

Discussion

In this nationwide population-based study**,** with nearly complete registration of dispensed medication, we found an overall 8.2% prevalence of antidepressants use among pregnant women in Iceland in 2003-2012. Use of antidepressants decreased with each passing trimester of pregnancy and new users in 2nd and 3rd trimesters were less than 1%. In one third of exposed pregnancies, women also dispensed anxiolytics, hypnotics or sedatives and such co-medication was most common in pregnancies exposed to TCAs. Sertraline, fluoxetine, escitalopram and paroxetine were the most commonly used antidepressants in the population, with a marked decrease in use of paroxetine during the study period.

This is the first study to thoroughly describe the use of all antidepressant substances among pregnant women in Iceland. In general the use of antidepressants and other psychotropic drugs is very high in Iceland in comparison with other countries,[10] both among adults and children.[18, 35, 36] It is difficult to assert why use of antidepressant is higher among pregnant women in Iceland than in its neighboring countries, as the actual underlying depression may not necessarily vary much by geography, e.g. between Nordic countries. We assume the explanations for this relatively high use of antidepressants in Iceland is related to factors, such as the education and culture of physicians who prescribe these and other psychotropic drugs, lack of reimbursement for non-pharmacological treatment options and other national characteristics.

Although the use of paroxetine decreased from 2% to 0.8% during the study period, its use remained higher in 2012 than expected, as national guidelines[37] advise against the use of paroxetine during pregnancy due to documented teratogenic effects.[32, 33]

The prevalence of antidepressant use during pregnancy had a u-shaped association with age, were women younger than 25 years and older than 35 years had higher prevalence. Most previous studies, however, suggest higher prevalence of antidepressant use among older pregnant women than younger.[6, 16, 38, 39] On the other hand when the data were stratified by age and parity simultaneously, we found that the number of previous births was the leading contributing factor to the higher prevalence among older women and the association with age was modest. In line with previous study results,[11] single women in Iceland were more likely to use antidepressants during pregnancy than their counterparts who cohabited with their partner. Interestingly, we also found that women of foreign citizenship were less likely to use antidepressants than women with Icelandic citizenship (2.4% vs. 8.8%), which raises the questions whether women of foreign citizenship in Iceland have poorer access to the healthcare during pregnancy; whether the wide difference in use could be related to cultural attitudes towards drug treatment or if it is due to less underlying depression in women of foreign citizenship in Iceland.

The prevalence of antidepressants use was higher in the first years of the study and rose again after 2010. This concurs with the general trend in Iceland showing rising antidepressant use after 2010,[18] which could possibly be linked to the aftermaths of the Icelandic economic collapse that hit the nation hard in late 2008. A few studies have been conducted to research if the consequences of the collapse did have any impact on national health outcomes.[40-42] Two recently published studies demonstrate increased prevalence of pregnancy induced hypertension[41] and low birth-weight deliveries following the collapse, particularly among young mothers (<25 years).[42] Further investigation of the potential effects of the economic collapse and following recession on mental health among pregnant women is thus warranted.

In line with previous studies, prevalence of dispensed antidepressants decreased from before pregnancy through each trimester from 6.1% before LMP to 2.9% in the third trimester. Although our study has a higher prevalence, the relative decrease is similar to a recent study among women in the Nordic countries.[11] We found that the prevalence of

women that were not dispensed an antidepressant until in the second and third trimester of pregnancy was 0.8%. This reflects that most women, who take antidepressants during pregnancy, will have started treatment before they became pregnant or very early in the pregnancy. Many studies have been conducted on possible adverse birth outcomes associated with antidepressants use (especially SSRIs). Two recent studies from the Nordic countries and the United States, demonstrate little or no increased risk of cardiac malformation with use of SSRI and venlafaxine[19] or antidepressants[5] in early pregnancy. Other studies have demonstrated a relation between exposure to SSRIs during late pregnancy and the risk for persistent pulmonary hypertension,[16, 43] although recent data suggest the risk is smaller than previously shown.[20] No significant association has been shown between the intake of SSRIs during pregnancy and perinatal death.[44, 45] To date, much less evidence exists about the potential long-term consequences of in-utero exposure to antidepressants, although recent studies have suggested a higher incidence of autism spectrum disorder among children born to women using SSRIs during pregnancy.[23, 24]

Study Strengths and Limitations

Our study covers the entire population of pregnant women in Iceland who gave birth after gestational week 22 and virtually every dispensed antidepressant to this population over a 10-year period. This study has several limitations worth mentioning. Firstly, the National Medicine Registry does not have information about the underlying diagnosis so we do not know if the antidepressants are prescribed for depression or other related conditions. Secondly, among women dispensed an antidepressant before becoming pregnant we do not know when exactly treatment started, as the study data only cover the period from three months before LMP until delivery. Finally, and similar to most registry based studies, we did not know whether the women actually consumed the dispensed drug during pregnancy or in each relevant trimester.

Conclusions

Use of antidepressants, mainly SSRIs, is relatively high among pregnant women in Iceland as compared to use during pregnancy in neighboring countries. Yet, the use decreases with each trimester and treatment initiation from 2nd trimester and onwards is rare in Iceland. Although use of drugs with known teratogenic effects (paroxetine) has decreased over time they were still being used by little under 1% of the pregnant population in 2012.

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Table 1. Prevalence of antidepressants use during pregnancy by maternal characteristics and drug group

	Any AD		SSRI		SNRI		TCA		Other AD	
	N	Prev	N	Prev	N	Prev	N	Prev	N	Prev
Total population	44775									
Total	3658	(8.2)	3158	(7.0)	398	(0.9)	247	(0.6)	241	(0.5)
Age (years)										
Mean age	29.1	(±5.8)	29.0	(±5.8)	29.1	(±5.5)	30.0	(±6.2)	29.3	(±5.7)
≤ 19	143	(9.4)	128	(8.6)	8	(0.5)	10	(0.7)	5	(0.3)
20 - 24	724	(8.9)	627	(7.7)	79	(1.0)	44	(0.5)	46	(0.6)
25 - 29	1096	(7.5)	952	(6.5)	133	(0.9)	63	(0.4)	78	(0.5)
30 - 34	964	(7.6)	836	(6.6)	106	(0.8)	68	(0.5)	62	(0.5)
35 - 39	590	(9.2)	497	(7.7)	61	(1.0)	53	(0.8)	42	(0.7)
≥40	141	(10.0)	118	(8.4)	11	(0.8)	9	(0.6)	8	(0.6)
Relationship status										
Single	956	(14.4)	823	(12.4)	116	(1.7)	70	(1.1)	60	(0.9)
Parental Cohabitation	2638	(7.0)	2276	(6.1)	279	(0.7)	174	(0.5)	174	(0.5)
Missing	64	(10.8)	59	(9.9)	3	(0.5)	3	(0.5)	7	(1.2)
Citizenship										
Icelandic	3557	(8.8)	3072	(7.6)	387	(1.0)	242	(0.6)	232	(0.6)
Non Icelandic	101	(2.4)	86	(2.0)	11	(0.3)	5	(0.1)	9	(0.2)
Place of delivery										
Capital	2605	(8.2)	2270	(7.1)	272	(0.9)	171	(0.5)	165	(0.5)
South region	141	(7.9)	116	(6.5)	18	(1.0)	8	(0.4)	19	(1.1)
Southwest region	168	(8.4)	148	(7.4)	17	(0.8)	11	(0.5)	10	(0.5)
North region	391	(8.5)	328	(7.1)	51	(1.1)	31	(0.7)	21	(0.5)
West region	236	(7.4)	202	(6.3)	26	(0.8)	16	(0.5)	17	(0.5)
East region	81	(11.8)	63	(9.2)	10	(1.5)	8	(1.2)	8	(1.2)
Other	36	(5.8)	31	(5.0)	4	(0.6)	2	(0.3)	1	(0.2)
Parity										
0	1250	(7.0)	1076	(6.0)	139	(0.8)	87	(0.5)	85	(0.5)
1	1202	(7.8)	1054	(6.8)	126	(0.8)	66	(0.4)	72	(0.5)
2	834	(9.8)	707	(8.3)	81	(0.9)	60	(0.7)	65	(0.8)
> 2	387	(13.8)	321	(11.5)	52	(1.9)	34	(1.2)	19	(0.7)
Delivery year										
2003 - 2005	1092	(8.7)	916	(7.3)	118	(0.9)	85	(0.7)	88	(0.7)
2006 - 2008	1055	(7.7)	913	(6.7)	126	(0.9)	70	(0.5)	62	(0.5)
2009 - 2012	1511	(8.1)	1329	(7.1)	154	(0.8)	92	(0.5)	91	(0.5)
Delivery month										
January – April	1154	(8.1)	1006	(7.0)	125	(0.9)	73	(0.5)	84	(0.6)
May - August	1286	(8.3)	1116	(7.2)	139	(0.9)	85	(0.5)	73	(0.5)
September - December	1218	(8.2)	1036	(6.9)	134	(0.9)	89	(0.6)	84	(0.6)

Prev = Prevalence per 100 pregnancies, with at least one dispensed antidepressant during pregnancy, including 90 days period before LMP
Any AD = any antidepressant
SSRI = Selective serotonin reuptake inhibitors
SNRI = Selective norepinephrine reuptake inhibitors
TCA = Tricyclic antidepressants
Other AD = Other antidepressants
N = Number

Table 2. Prevalence of the most commonly used antidepressants substances by trimester of pregnancy

Trimester	Before LMP	1st trimester	2nd trimester	3rd trimester	Anytime during pregnancy
	N Prev	N Prev	N Prev	N Prev	N Prev
Any antidepressant	2735 (6.1)	2032 (4.5)	1595 (3.6)	1297 (2.9)	3658 (8.2)
SSRI	2212 (4.9)	1753 (3.9)	1470 (3.3)	1213 (2.7)	3158 (7.1)
Sertraline	752 (1.7)	715 (1.6)	710 (1.6)	605 (1.4)	1419 (3.2)
Fluoxetine	496 (1.1)	404 (0.9)	397 (0.9)	302 (0.7)	832 (1.9)
Escitalopram	468 (1.0)	331(0.7)	152 (0.3)	110(0.2)	588 (1.3)
Paroxetine	342 (0.8)	257 (0.6)	171 (0.4)	147 (0.3)	431 (1.0)
Citalopram	202 (0.5)	133 (0.3)	67 (0.1)	54 (0.1)	260 (0.6)
SNRI	314 (0.7)	198 (0.4)	83 (0.2)	57 (0.1)	398 (0.9)
Venlafaxine	246 (0.5)	157 (0.4)	67 (0.1)	48 (0.1)	314 (0.7)
Duloxetine	71 (0.2)	41 (0.1)	16 (0.04)	9 (0.02)	88 (0.2)

Prev = prevalence 100 pregnancies ,with at least one dispensed antidepressant
SSRI = Selective serotonin reuptake inhibitors
SNRI = Selective norepinephrine reuptake inhibitors

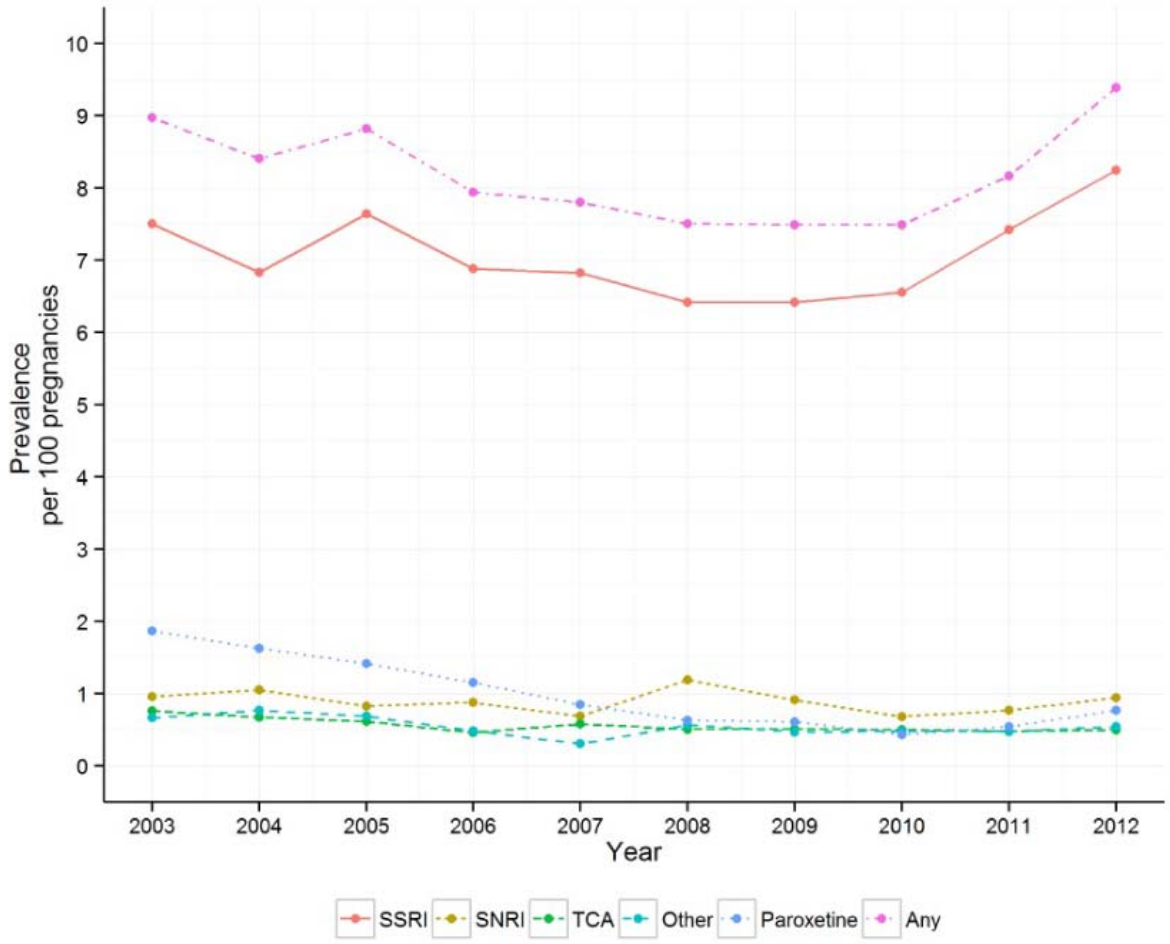

Figure 1. Prevalence * of antidepressant use in pregnancy per 100 pregnancies by drug group and year of delivery.

*At least one dispensed antidepressant during pregnancy, including 90 days period before LMP
SSRI = Selective serotonin reuptake inhibitors
SNR I = Selective norepinephrine reuptake inhibitors
TCA = Tricyclic antidepressants

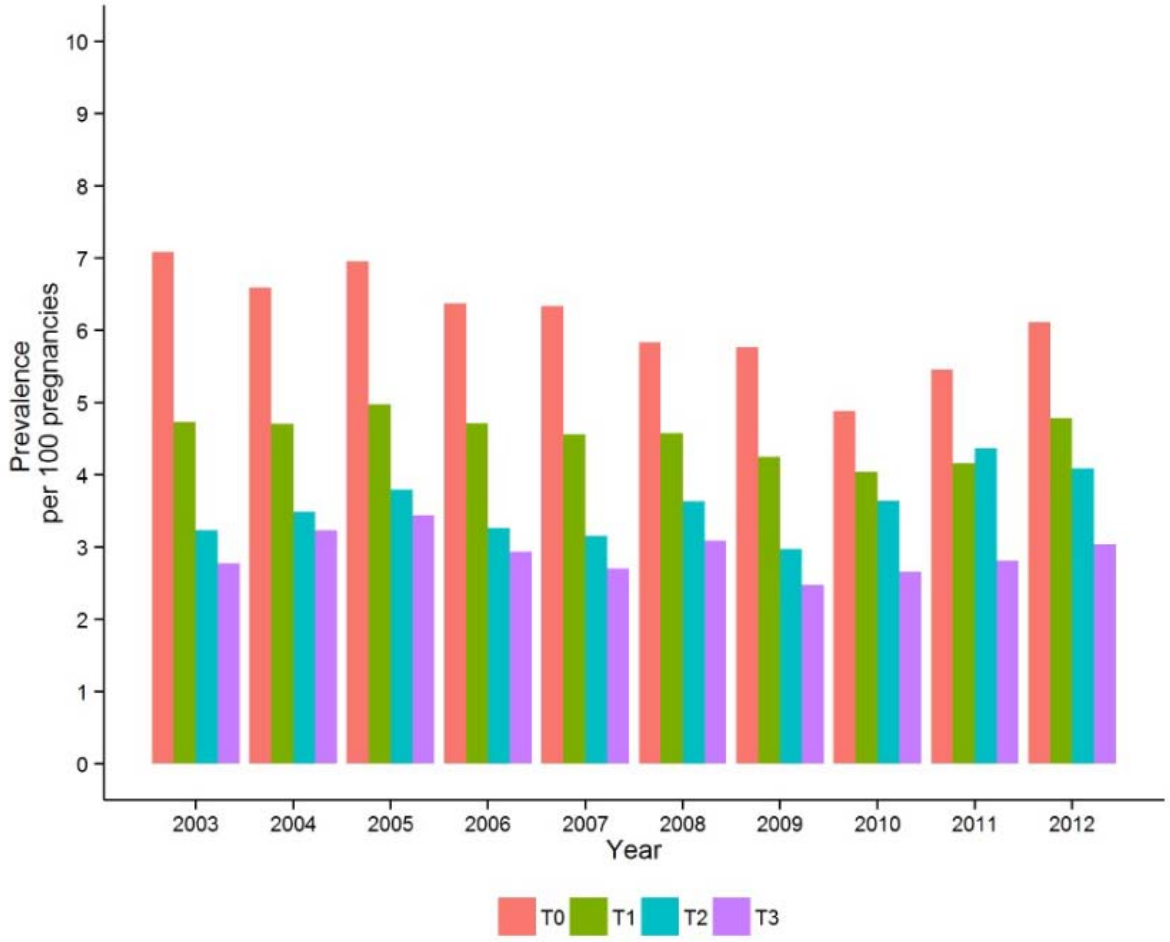

Figure 2. Prevalence of antidepressant use in pregnancy per 100 pregnancies by trimester.

T0 = up to 90 days before LMP
T1 = 1st trimester
T2= 2nd trimester
T3 = 3rd trimester

Supplementary Table 1. Categorization of antidepressants with defined daily doses (DDDs) for each substance

Drug	ATC Class	DDD (mg)	Date of marketing authorization
Any antidepressant	N06		
SSRIs	N06AB		
Citalopram	N06AB04	20 mg	1.4.1993
Ecitalopram	N06AB10	10 mg	1.8.2002
Fluoxetine	N06AB03	20 mg	1.6.1998
Paroxetine	N06AB05	20 mg	1.4.1993
Sertraline	N06AB06	50 mg	1.10.1995
SNRIs	N06AX		
Venlafaxine	N06AX16	0.1 g	1.10.1998
Duloxetine	N06AX21	60 mg	1.10.1998
TCAs	N06AA		
Clomipramine	N06AA04	0.1 g	1.3.1977
Trimipramine	N06AA06	0.15 g	1.10.1995
Amitriptyline	N06AA09	75 mg	1.12.1972
Nortriptyline	N06AA10	30 mg / 75 mg	1.1.1985
Doxpin	N06AA12	0.1 g	1.12.1972
Other antidepressants			
Moclobemide	N06AG02	0.3 g	1.10.1990
Mianserin	N06AX03	0.15 g	1.1.1994
Mirazapine	N06AX11	30 mg	1.12003
Bupropionum	N06AX12	0.3 g	1.9.2000
Reboxetine	N06AX18	8 mg	1.6.2000

ATC = Anatomical Therapeutic Chemical classification
DDD = Defined daily dose
SSRI = Selective serotonin reuptake inhibitors
SNR I = Selective norepinephrine reuptake inhibitors
TCA = Tricyclic antidepressants

Supplementary Table 2. Number and proportion of pregnancies exposed to antidepressants with co-medication* of anxiolytics, hypnotics and sedatives by drug group

	Any AD	SSRI	SNRI	TCA	Other AD
	N %	N %	N %	N %	N %
Total	3658	3158	398	247	241
Overall anxiolytics	705 (19.3)	516 (16.3)	73 (18.3)	60 (24.3)	56 (23.2)
Overall hypnotics/sedatives	657 (17.9)	466 (14.7)	81 (20.3)	60 (24.3)	50 (20.7)
Anxiolytics or hypnotics/sedatives	1106 (30.2)	805 (25.5)	124 (31.1)	94 (38.1)	83 (34.4)

SSRI = Selective serotonin reuptake inhibitors
SNRI = Selective norepinephrine reuptake inhibitors
TCA = Tricyclic antidepressants
Other AD= Other antidepressants
*Medications used concurrant to antidepressants

Appendix – Study Approvals

Miðstöð í lýðheilsuvísindum
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Reykjavík, 16. maí 2013
Tilvísun: 2009010039ÞS/--

Efni: Norræn samanburðarrannsókn á SSRI-lyfjanotkun á meðgöngu og áhrifum á fæðingarútkomur

Persónuvernd vísar til bréfs yðar, dags. 20. desember 2012, varðandi rannsóknina „SSRI lyfjanotkun á meðgöngu og áhrif á fæðingarútkomur: Norræn samanburðarrannsókn". Byggist lögmæti vinnslu persónuupplýsinga í þágu þeirrar rannsóknar á leyfi Persónuverndar, dags. 23. september 2009, og er nú óskað eftir framlengingu á því leyfi.

Í bréfi yðar segir nánar að við umrætt, norrænt rannsóknarsamstarf sé byggt á gögnum úr lýðgrunduðum lyfjagagnagrunnum um yfir 1,6 milljón fæðinga á Norðurlöndunum. Rannsakendur hafi nú hug á áframhaldandi rannsóknum sem nái yfir tímabilið 2003–2012 í tengslum við þetta verkefni þar sem vansköpun barna verði m.a. höfð sem útkoma. Hafi rannsakendur á hinum Norðurlöndunum nú sótt sótt um leyfi hjá viðeigandi stofnunum til að framlengja rannsóknartímabilið út árið 2012. Sem ábyrgðarmaður fyrir Íslands hönd óskið þér því eftir samþykki Persónuverndar til slíks hins sama. Fæli það í sér endurtekna samkeyrslu íslenskra gagna úr fyrrgreindum skrám fyrir öll rannsóknarárin 2003–2012, en samkeyrslan færi fram innan veggja Landlæknisembættisins. Þá kemur fram að niðurstöður samkeyrslunnar yrðu aftengdar persónuauðkennum.

Að auki er í bréfi yðar óskað eftir leyfi Persónuverndar til að nýta íslensku gögnin sérstaklega til að lýsa SSRI-lyfjanotkun barnshafandi kvenna á Íslandi, en gögnin yrðu án persónuauðkenna. Þessi notkun gagnanna færi fram á Miðstöð í lýðheilsuvísindum við Háskóla Íslands með sömu innlendu samstarfsaðilum og koma að hinu samnorræna rannsóknarsamstarfi, þ.e. dr. Helga Zoëga, lektor í lýðheilsuvísindum við Læknadeild Háskóla Íslands, og Ragnheiði I. Bjarnadóttur,

umsjónarmanni Fæðingaskrár og fæðinga- og kvensjúkdómalækni á Kvenna- og barnasviði Landspítala, auk yðar og eins eða tveggja meistaranema í lýðheilsuvísindum.

Með vísan til 1. og 7. tölul. 1. mgr. 4. gr. reglna nr. 712/2008 um tilkynningarskylda og leyfisskylda vinnslu persónuupplýsinga, sbr. 33. gr. laga nr. 77/2000 um persónuvernd og meðferð persónuupplýsinga, gerir Persónuvernd ekki athugasemdir við fyrirhugaða framlengingu á rannsóknartímabili og viðbót við rannsóknina. Hins vegar er gert að skilyrði að við þá viðbót verði í einu og öllu farið að skilmálum framangreinds leyfis stofnunarinnar til vinnslu persónuupplýsinga vegna rannsóknarinnar, dags. 23. september 2009. Minnt er á að samkvæmt b-lið 5. gr. III. kafla leyfisins ber að eyða öllum rannsóknargögnum eigi síðar en **1. október 2014.** Þá er minnt á ákvæði b-liðar 2. gr. sama kafla leyfisins þar sem mælt er fyrir um að fá skuli þagnarskylduyfirlýsingar frá háskólanemum og öðrum þeim sem ekki teljast til heilbrigðisstétta og taka þátt í framkvæmd rannsóknarinnar.

Að lokum er beðist velvirðingar á töfum sem orðið hafa á meðferð málsins, en þær stafa af fækkun starfsmanna og miklum önnum Persónuverndar.

Virðingarfyllst

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Reykjavík 15. janúar 2013
Tilv.: VSNb2008100028/03.7

Efni: 08-144-V1 SSRI lyfjanotkun á meðgöngu og áhrif á fæðingarútkomur: Norræn samvinnurannsókn. (e. SSRI´s and adverse Effects on Off-Spring: A Nordic Collaborative Study).

Á fundi sínum 15.01.2013 fjallaði Vísindasiðanefnd um umsókn þína dags. 14.12.2012, vegna viðbótar við ofangreinda rannsóknaráætlun. Í bréfi þínu segir:

"...óska hérmeð eftir um leyfi fyrir að framlengja rannsóknartímabilið og vinnslu gagna vegna rannsóknarinnar SSRI lyfjanotkun á meðgöngu og áhrif á fæðingarútkomur: Norræn samvinnurannsókn (e. SSRIs and Adverse Effects on Offspring: A Nordic Collaborative Study) út árið 2012. Hinn 13. janúar 2009 veitti Vísindasiðanefnd leyfi til rannsóknarinnar (Tilv: VSNb2008100028/03.7) sem byggði á fyrirliggjandi gögnum um barnshafandi konur á Íslandi á árunum 2003 til 2007 úr Fæðingaskrá, Lyfjagagnagrunni, Dánarmeinaskrá og Vistunarkrár heilbrigðisstofnana (1999-2007). Börn ofantaldra kvenna fædd á þessu árabili voru einnig hluti af rannsókn og var upplýsingum um hvert þeirra fylgt eftir í eitt ár eftir fæðingu. Þegar hafa verið unnar tvær vísindagreinar úr þessu verkefni:

1. *Selective Serotonin Reuptake Inhibitors during pregnancy and risk of stillbirth and infant mortality.*
   *Stephansson O, Kieler H, Haglund B, Artama M, Engeland A, Furu K, Gissler M, Nørgaard M, Nielsen RB, **Zoëga H, Valdimarsdóttir U**.*
   Accepted, JAMA (in November 2012).

2. *Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries.*
   *Kieler H, Artama M, Engeland A, Ericsson O, Furu K, Gissler M, Nielsen RB, Nørgaard M, Stephansson O, **Valdimarsdottir U, Zoega H**, Haglund B.*
   BMJ. 2012 Jan 12;344:d8012. doi: 10.1136/bmj.d8012. (sjá meðfylgjandi)

Rannsóknarsamstarfið byggði á gögnum úr lýðgrunduðum lyfjagagnagrunnum og yfir 1,6 milljón fæðinga á Norðurlöndunum. Telja má víst að hvergi í heiminum megi finna sambærilegt tækifæri til að kanna sjaldgæfar lyfjaútkomur með þessum hætti. Rannsakendur nú hafa hug á áframhaldandi rannsóknum sem nær yfir tímabilið 2003-2012 í tengslum við þetta verkefni þar sem vansköpun barna verður m.a. höfð sem útkoma.

Aðrar Norðurlandaþjóðir hafa nú sótt um leyfi hjá viðeigandi stofnunum um að framlengja rannsóknтímabilið út árið 2012. Sem ábyrgðarmaður fyrir Íslands hönd óskar undirrituð því hérmeð eftir samþykki Vísindasiðanefndar til slíks hins sama. Myndi þetta fela í sér endurtekna samkeyrslu íslenskra gagna úr fyrrgreindum skrám fyrir öll rannsóknarárin 2003-2012. Samkeyrsla ætti sér stað eftir sem áður á Embætti landlæknis. Ábyrgðarmaður myndi í kjölfarið senda samtengd og með öllu ópersónugreinanleg gögn til Svíþjóðar fyrir gagnavinnslu.

Í ljósi einstaks efniviðs og mikillar vinnu sem sem á sér stað vegna samkeyrslu óskar undirrituð jafnframt eftir leyfi Vísindasiðanefndar til að nýta íslensku gögnin sérstaklega til að lýsa SSRI lyfjanotkun barnshafandi kvenna á Íslandi. Þetta hefur ekki verið gert áður en myndi án efa leiða af sér mikilvæga þekkingu hér innanlands (sjá meðfylgjandi rannsóknaráætlun). Yrði þessi undirrannsókn framkvæmd í Miðstöð í lýðheilsuvísindum við Háskóla Íslands með sömu innlendum samstarfsaðilum (Dr. Helga Zoëga lektor í lýðheilsuvísindum við Læknadeild Háskóla Íslands og Ragnheiði I. Bjarnadóttur, fæðinga- og kvensjúkdómalæknir, á Kvenna- og barnasviði, Kvennadeild, Landspítala, umsjónarmaður Fæðingaskrár), auk 1-2 meistaranema í lýðheilsuvísindum."

Vísindasiðanefnd hefur farið yfir bréf þitt og gerir ekki athugasemdir við tilgreindar breytingar. Viðbót nr. 1 ásamt fylgigögnum við ofangreinda rannsókn, er endanlega samþykkt af Vísindasiðanefnd.

Áréttað er að ábyrgðarmanni ber að láta stofnanir, sem áður hafa veitt leyfi vegna framkvæmdar rannsóknarinnar, vita af ofangreindri breytingu á rannsóknaráætluninni.

Með kveðju,
f.h. Vísindasiðanefndar,

Gísli Ragnarsson

Gísli Ragnarsson, varaformaður