SHORT COMMUNICATION

A UNIQUE OPPORTUNITY TO STUDY SHORT- AND LONG-TERM CONSEQUENCES IN CHILDREN PRENATALLY EXPOSED TO ILLICIT DRUGS AND OPIOID MAINTENANCE TREATMENT USING CZECH AND SCANDINAVIAN REGISTERS

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SUMMARY

Licit and illicit drug use in pregnant women constitutes a long lasting and serious problem worldwide. Information on long-term effects of maternal drug use on the child is limited. Nationwide registers provide a great potential to study short- and long-term consequences for children exposed to licit and illicit drugs during pregnancy. We discuss this potential, with a special emphasis on exposure to methamphetamine, heroin and prescription drugs used for opioid maintenance treatment (OMT). We also discuss the advantages of analysis using register data and of merging such data from different regions. The Czech and Scandinavian registers are largely comparable and provide great opportunities to conduct innovative research. For instance, using Czech and Scandinavian cohorts we can compare groups with similar characteristics, such as mothers in OMT and mothers addicted to other drugs while also controlling for important confounding factors such as health and socioeconomic status.

Key words: national health registry, registry-linkage study, drug use, opioid maintenance treatment, methamphetamine, children, pregnancy

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INTRODUCTION

Licit and illicit drug use during pregnancy may have negative effects on the foetus. Opioids and stimulants constitutes a long lasting and increasing problem worldwide associated with high costs to society and at the personal level for the women and children involved (1).

The average annual prevalence of problematic use of opioids among adults in Europe was around 0.4%, the equivalent of 1.3 million in 2012 (2). Heroin is the most frequently used opioid in Europe. At national levels, the estimated prevalence of opioid use ranges from less than 0.1% to around 0.8% among persons aged 15–64, women constitute about 20% of this group, the majority of them in childbearing age (2).

The use of amphetamine-type drugs (amphetamine and methamphetamine) is typical for the Czech Republic and Scandinavian countries and is on the rise worldwide (2, 3). In Europe, among persons aged 15–64 about 29% are women, the majority in childbearing age (2).

Heroin use during pregnancy is associated with a number of negative consequences for the baby such as reduced birth parameters and heroin withdrawal symptoms after birth (4). Long-term negative outcomes including physical and mental developmental impairments have also been reported (5). Illicit (meth)amphetamine use during pregnancy has received relatively little attention because prevalence of use during pregnancy is generally lower than for heroin, cocaine and other narcotics. Recent studies suggest that amphetamine use during pregnancy is associated with a higher than expected risk of heart defects, gastroschisis and small intestinal atresias, and cleft lip and palate. However, these studies did not investigate outcomes from (meth)amphetamine use alone (6). There is little evidence on the long-term consequences of use of (meth)amphetamine during pregnancy. Children exposed to (meth)amphetamine in utero show decreased arousal, increased stress, decreased school achievements, movement disturbances, and they have lower scores on sustained attention, long-term spatial and verbal memory, and visual motor integration (7). However, current

knowledge on the consequences of methamphetamine abuse during pregnancy is limited and there is a need for further research.

Opioid Maintenance Treatment (OMT) has become mainstream treatment modality for heroin addicts (8), ~734,000 opioid users received OMT in 2012 in the EU (2). Methadone was prescribed to approximately two-thirds of the patients, while approximately 20% received buprenorphine as the medication in OMT (2). Both methadone and buprenorphine have been prescribed to opioid-dependent pregnant women for years; the drugs contribute to improved obstetric and perinatal outcomes compared to heroin use during pregnancy (4). Once stabilized on OMT, women are better equipped to benefit from psychosocial treatment and receive help to deal with other problems associated with substance abuse. However, both methadone and buprenorphine may have negative effects. About 47–90% of children prenatally exposed to these drugs show signs of neonatal abstinence syndrome (NAS) (9, 10). In addition to NAS, OMT seems to be associated with other negative short-term outcomes such as lower growth parameters (length, weight and head circumference), methadone more so than buprenorphine (11). Exposure to OMT during pregnancy may also be associated with long-term outcomes, such as cognitive development (12, 13), problems with motor skills (14, 15), and possibly also social skills (16). However, long-term developmental outcomes after OMT have not yet been adequately researched.

Pregnant female (meth)amphetamine users do not receive prescription drug treatment for their (meth)amphetamine addiction. Instead, the treatment usually includes detoxification and referral to outpatient or inpatient treatment at institutions specialized in treating pregnant women using illicit drugs and their young children.

The treatment initiation and adherence in pregnant illicit drug users are complicated by factors related to both the patients and the treatment providers, such as delays in treatment referral, fear of adverse effects of treatment and stigmatization due to illicit drug use (17).

Challenges Faced in Studies of Drug Use in Pregnant Women

In the Introduction section, we presented results from previous research. Many studies have limitations and therefore the results on short- and long-term effects of illicit drugs or OMT are not conclusive. Detecting the unique effects of prenatal illicit drug and OMT drug exposure is difficult. Challenges include:

- Populations of pregnant women with illicit drug use problems are relatively small in each country. For instance, in Norway, about 30–45 women undergoing OMT give birth to children each year (18). Thus, statistical power to study effects of illicit drugs is correspondingly weak.
- It is difficult to get in contact with, recruit and retain a population of pregnant women using illicit drugs or receiving OMT in clinical studies.
- Several studies have used only self-report data when studying pregnant women with substance use problems (19). A challenge with this approach is the longstanding controversy on the validity of attitudinal reports in addiction research.
- Studies on pregnant women with illicit drug use need to take into account several confounding factors. Multiple risk factors exist for illicit drug use such as past or present addictions to other drugs including alcohol and tobacco, homelessness, poverty, poor nutrition, psychological illness, sexual or physical abuse, and young age (19, 20). Additional demographic factors include nationality, marital status and health status.
- Choosing the best control group. Comparing pregnant women with substance use problems with a population of all other pregnant women may be problematic because the two populations differ with respect to many factors such as comorbidity and life style.
- Most addicted individuals use several drugs. This complicates measuring the direct effect of the illicit drug of interest.
- Populations with substance use problems use also other prescription drugs, both with and without abuse potential (21). This complicates separating the direct effect of the illicit drugs from the effect of prescribed drugs.
- Difficulties with identifying children in follow up studies. Many of these children will have moved to foster care.

Nationwide Registers

Both the Czech Republic and the Scandinavian countries have nationwide registers with civil registration numbers, which enables linkage of data between different registers on a personal level, and on a family level such as between mother and child.

In the Czech Republic, 1,008,821 women gave birth to 1,027,200 newborns between years 2000–2009. Of these 60,502 were officially registered as tobacco smokers, 1,528 alcohol users and 1,836 illicit drugs users during pregnancy (22).

In Scandinavia, the estimated number of women in OMT was 1,200 among nearly 1.9 million pregnant women in the period 1997–2014.

Relevant Health Registers in the Czech Republic

The Czech national health registers administered by the Institute of Health Information and Statistics of the Czech Republic include:

The National Register of Drug Users in Treatment includes data on patients starting and terminating addiction (including substitution) treatment, records are ICD-10 based.

The National Register of Reproduction Health includes information on the mothers at childbirth, during pregnancy and delivery. Another part includes information on children during childbirth or puerperium, such as therapy during and after birth, and status of the newborn. Further part of this register collects information on congenital malformations detected in children up to 15 years of age, in foetuses in the course of pregnancy and malformations in stillbirths.

The National Register of Hospitalized Patients is a nationwide population register that includes information on hospitalization irrespective of the type of admission and termination (discharge, transfer, death).

The Information System on Deaths is a general mortality register of the Czech Republic.

The Information System of Infectious Diseases (EPIDAT) include information on all notifications of selected serious infections – verified cases, suspected diseases, carrier of an infection, and deaths. Some infections are not monitored in this system since there are separate registers for them.

The Register of Venereal Diseases includes information on all notifications of verified venereal disease, suspected venereal disease, and deaths due to venereal disease.

The Register of Tuberculosis monitors all persons with detected active tuberculosis or other mycobacteriosis.

The National Oncology Register provides data on cancer cases diagnosed and provides follow-up information on each case.

Relevant Registers in the Scandinavian Countries

All Scandinavian countries have national registers, which include prospectively collected information on the health of all inhabitants using unique personal identifiers facilitating linkage between registries.

The Prescription Databases. All Scandinavian prescription databases include electronically submitted information on all prescribed drugs dispensed to all individual outpatients in the respective countries.

The Scandinavian Birth Registries include information on complications during pregnancy and delivery, length of pregnancy and information on the infant, including birth defects and other perinatal problems, information on the mother's health and lifestyle during the pregnancy.

The Patient Registries include information on admission to hospitals and specialist health care, such as date of admission and discharge, primary and secondary diagnosis according to ICD-10, information on comorbidities

The Norwegian Directorate of Health administers a database that includes information on diagnoses (ICPC codes) that were the cause of contact between patient and primary health care (physicians, psychologists, physiotherapist, etc.) and date of the visit.

The Scandinavian Cause of Death Registries include information on the cause of death (ICD-10 based) for individuals who were residents of the country at the time of death.

Socio-economic data from Statistics Norway, Sweden and Denmark include information on marital status, education, income, employment, and social security of pregnant women.

Collaboration between Czech and Scandinavian Research Teams

The aim of the foreseen project between Norway and the Czech Republic is to study cohorts of women using illicit drugs with focus on methamphetamine and heroin and women receiving OMT during pregnancy. The Norwegian research group also collaborates with colleagues from Sweden and Denmark, thus facilitating a Scandinavian cohort of women in OMT. The Scandinavian countries and the Czech Republic have received ethical approval for linkage of data to create de-identified (encrypted) research files.

We are interested in both neonatal and long-term consequences for the child. The overarching objective is to describe both cohorts of pregnant women using illicit drugs or prescription drugs used in OMT with respect to comorbidity (somatic and psychiatric) and socioeconomic status.

The main objective is to study adverse pregnancy outcomes, adverse neonatal and long-term outcomes in children exposed to illicit drugs (Czech setting) or OMT drugs (Scandinavian and Czech setting) during foetal life. The Czech and the Scandinavian cohorts will be used to compare findings related to effects of illicit drugs and prescription drugs used in OMT.

A database-linkage retrospective cohort study will be conducted applying national health registries. The registries in the Czech Republic cover approximately 10.5 million inhabitants.

The registries in Norway, Denmark and Sweden cover more than 21 million inhabitants. The Scandinavian cohort comprises the largest population of pregnant women in OMT and their children to date. All pregnant women who, according to prescription registries in Norway, Sweden and Denmark, used OMT drugs during pregnancy in the period 1997–2014 will be included in the study.

Possibilities with Observational Studies Using Registry Linkage Data

Pregnant women who use illicit drugs are a vulnerable group who has not been much researched until now. Additionally, most of the research on pregnancy and illicit drug use and/or OMT has been conducted in the US, where socioeconomic factors such as homelessness and poverty among opioid dependent individuals may be confounding factors (20). In the Scandinavian countries all inhabitants are covered by a tax-funded National Insurance System and have equal access to free health care and education. The situation in the Czech Republic is similar. While pregnant women who use illicit drugs or receive OMT often belongs to low-income families, they are not necessarily homeless or experience the same degree of poverty as many drug users in the US. With regards to OMT in Norway, opioid dependent women have typically been in OMT for about two years prior to becoming pregnant, they stay in treatment for a long time and the use of illicit substances and alcohol during pregnancy is low (10, 23). These factors distinguish the pregnant women in OMT in Norway from women in previous studies. On the other hand, women are similar with regard to frequency and extent of smoking during pregnancy and the substantial somatic and psychological problems (19, 23).

The National Health Registry data from the Czech Republic and Scandinavian countries enable studying effects from licit and illicit drug use, and/or drugs used for OMT among pregnant women. These unique datasets overcome some of the challenges in studies of pregnant women mentioned above. For instance, by combining data from more countries, statistical power is increased, which again increases the chance that low prevalence risk patterns in data are detected. Further, the unique identification numbers enable linkage of data from several registers in all partner countries. This has several advantages. For example, it allows for inclusion of important confounders such as ethnicity, socioeconomic characteristics and health status. A few concrete examples from the Czech setting are linkage of data in the National Register of Reproduction Health, National Register of Hospitalized Patients, National Register of Addiction Treatment, and the Information System on Deaths. This allows for identifying pregnant Czech women who have used illegal drugs or received OMT for a short or extended period during pregnancy. Further, data from the National Register of Reproduction Health, National Register of Hospitalized Patients, National Oncology Register, and the Information System of Infectious Diseases will be used to study long-term effects in the child of prenatal exposure to illegal drugs or OMT in the child.

In this short communication we have described relevant registry data sources and discussed the advantages of using registry

data in this field of research. A research collaboration that utilizes a Central European and a Scandinavian cohort has great potential in using cohorts from different parts of Europe to study even the low prevalence effects of drugs.

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Contributors

SS, MH, IOL and RG conducted the literature searches and performed the initial drafting of the manuscript. BN and VM contributed to literature searches and the writing and finalization of the manuscript. All authors have approved the final manuscript.

Conflict of Interests

None declared

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